In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 16-419V

(to be published)

CHRISTINA OSENBACH *and* BRYAN OSENBACH *parents of* B.O., *a minor*,	Chief Special Master Corcoran
Petitioners,	Filed: August 8, 2023
v.	
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	

Sylvia Chin-Caplan, Law Office of Sylvia Chin-Caplan, LLC, Boston, MA, for Petitioners.

Tyler King, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On April 4, 2016, Christina and Bryan Osenbach, on behalf of their minor child, B.O., filed a Petition under the National Vaccine Injury Compensation Program (the "Vaccine Program"[2]), alleging that as a result of receiving the pneumococcal and inactivated poliovirus ("IPV") vaccines on April 17, 2013, B.O.'s pre-existing, underlying epilepsy/seizure disorder was significantly aggravated. Petition (ECF No. 1) at 1. An entitlement hearing in the matter was held in Washington, D.C. on September 19, 2022.

[1] As provided by 42 U.S.C. § 300aa-12(d)(4)(B), the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire Decision will be available to the public in its current form. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C. §§ 300aa-10–34 (2012)) (hereinafter "Vaccine Act" or "the Act"). All subsequent references to sections of the Vaccine Act shall be to the pertinent subparagraph of 42 U.S.C. § 300aa.

Having reviewed the record, all expert reports, the medical records, and associated literature, I hereby deny an entitlement award. As discussed in greater detail below, Petitioners have not preponderantly established that the pneumococcal or IPV vaccine could aggravate B.O.'s neurological condition (which the record evidence suggests is best characterized as Dravet syndrome—a genetically-caused epileptic disorder).[3]

I. Factual Background

B.O.'s First Seizures (Prior to Relevant Vaccinations)

A year before the vaccinations in dispute, B.O.'s seizure disorder had clearly begun—and credible evidence supports the conclusion that vaccines played a role in the initial seizure (although those vaccines are not the basis for this claim).[4]

After a pregnancy complicated by gestational diabetes, B.O. was born on March 12, 2012. Ex. 11 at 73; Ex. 28 at 1. On July 25, 2012, B.O. received his four-month vaccinations—DTaP, Hep B, IPV, PCV, and rotavirus. Ex. 6 at 79–82. The next day—July 26, 2012—B.O. experienced his first seizure and presented to WakeMed ER. Ex. 13 at 96–99; Ex. 18 at 981–84, 1030–1040; Ex. 24 at 9–10. At 6:30 a.m., his parents noted that he was sweating, soaked in urine, lethargic, and hypotonic. Ex. 13 at 96; Ex. 18 at 1030. He began to become more interactive on the way to the emergency room ("ER"). Ex. 13 at 96; Ex. 18 at 1030. In the ER, B.O. was lethargic and demonstrated poor muscle tone in his head and upper extremities. Ex. 13 at 97; Ex. 18 at 1031. The ER physician indicated "[h]e may also be experiencing an adverse reaction [to] the DTaP which has been reported to rarely cause a hypotonia episode." Ex. 13 at 97; Ex. 18 at 1031. He had a normal MRI and his cerebrospinal fluid studies were unremarkable. Ex. 18 at 1009. There is no evidence from these records that B.O. experienced a fever in association with this seizure, however.

B.O. was then admitted to the Pediatric Intensive Care Unit ("PICU"), where he was seen by pediatric neurologist John Wooten, M.D. Ex. 13 at 93–94. B.O.'s parents recalled to Dr. Wooten that since birth, B.O. had displayed a right-side preference with his head, eyes, and face. *Id*. Dr. Wooten analyzed the situation and explained:

> In my opinion, there are multiple explanations for this scenario but the most likely scenario is preceding mild left hemiparesis with the immunizations being a physiologic trigger as a

[3] Dravet syndrome is a severe epilepsy of infancy also termed "Severe Myoclonic Epilepsy of Infancy," or "SMEI." *Faoro v. Sec'y of Health & Hum. Servs.*, No. 10-704V, 2016 WL 675491, at *1 (Fed. Cl. Spec. Mstr. Jan. 29, 2016).

[4] In fact, they could not be—since any claim based on vaccines B.O. received in July 2012 would have accrued (under the Act's three-year limitations period) by *July 2015*—almost a year before the claim was filed in April 2016 (although it is otherwise timely, given its focus on the April 2013 vaccines).

> stress, then causing perhaps a seizure in his sleep or subclinical seizure or even a metabolic event such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke) syndrome, or other type of catastrophic change leading to the current presentation . . . Concerning immunizations, I would withhold for now."

Id. at 94.

On August 1, 2012, B.O. was seen by his primary care physician Kristen Donoghue, M.D. Ex. 6 at 77. Dr. Donoghue noted that B.O. was recently admitted for seizure possibly due to immunizations, but was "[u]nclear whether vaccines may or may not be related." *Id.* Approximately two weeks later, B.O. had a follow-up appointment with Dr. Wooten. Ex. 13 at 85–87. Dr. Wooten noted that B.O. experienced the following:

> a very frightening apparent life-threatening event following immunizations. It consisted of poor responsiveness, possible seizure with left hemiparesis that persisted for a while, and a focal EEG. I discussed with the parents that this was most likely a seizure secondary to a stressful event I do not think It was a major reaction to the immunization itself with the immunization serving as a single stressful event He has had two immunizations now. which gives him some protective immunity although not ideal.

Id. at 87. Another electroencephalogram ("EEG") was recommended, and the results were abnormal. *Id*. at 84. This EEG showed some mild right sided slowing compared to the left, and some asymmetry that is similar to what was presented in the hospital at WakeMed. *Id*.

During the fall of 2012, B.O. experienced two additional seizures, both of which occurred outside the context of vaccination. Ex. 18 at 912–13, and Ex. 13 at 79 (October 2012 afebrile seizure, occurring while feeding); Ex. 19 at 74–77 (December 2012 afebrile and prolonged seizure after bath; no reported illness, although ear infection discovered thereafter); *see also* Ex. 1 (vaccination record). He was then evaluated at Duke Medical Center in February 2013 by pediatric neurologist Mohamad Mikati, M.D. Ex. 10 at 258–61; Ex. 17 at 6–8. At this time, a family history of seizures was discussed (including the experience of infantile/pediatric seizures). Ex. 10 at 260; Ex. 17 at 7. And although (as reflected above) the role initial vaccinations might have played in B.O.'s first seizures had been specifically addressed by prior treaters, in April 2013 Dr. Wooten informed the Petitioners of his view that (given the fact that B.O. had received some vaccines *without* seizures being triggered), the risk of seizures triggered by stress of vaccination could be reduced simply by increasing anti-seizure medication at the time of vaccination. Ex. 13 at 70.

During the winter of 2013, B.O. received additional vaccines on two separate occasions. *See* Ex. 1 (third dose of pneumococcal vaccine administered on January 29, 2013, and third dose

of Hep B vaccine administered on February 6, 2013). The record does not reveal any occurrence of seizures after these instances.

Seizures Following 2013 Vaccinations

On April 17, 2013, B.O. received the pneumococcal and IPV vaccines as part of his twelve-month physical. Ex. 6 at 54–57. At this time (and consistent with Dr. Wooten's advice), he had been administered increased dosages of anti-seizure medication. Ex. 18 at 824. The next day, B.O. was seen at the WakeMed ER after experiencing four seizures. *Id*. Because additional anti-seizure medication proved ineffective in arresting the seizure activity, a sedative was repeatedly administered intravenously, necessitating oral airway intubation for a respiratory arrest, and B.O. was ultimately transferred to a pediatric intensive care unit for continuing care. *Id.*; Ex. 24 at 39–40. An MRI was performed on April 19, 2013, that showed no intracranial or cortical base abnormalities. Ex. 18 at 757. There was noted mild mucosal thickening affecting the mastoid air cells bilaterally. *Id.* He was discharged on April 20th, and the summary contained in the discharge record took into account his history of vaccine-associated seizure activity. Ex. 18 at 764, 757.

B.O. was taken back to Dr. Wooten on April 25, 2013, who (and despite B.O.'s recent experiences) expressed the concern that B.O. was becoming behind in his vaccination schedule. Ex. 13 at 66. B.O.'s parents also returned to Duke Health to consult Dr. Mikati on May 22, 2013. Ex. 10 at 283–86; Ex. 17 at 20–23. Dr. Mikati noted the history of seizures following his four-month immunizations, with the most recent seizure occurring the day after receipt of his April 17, 2013 vaccines. Ex. 10 at 283–86; Ex. 17 at 20–23. Dr. Mikati also indicated at this time that "[n]o vocalization [was] heard[,]." Ex. 10 at 285–86; Ex. 17 at 22–23.

Concerns about B.O.'s development were expressed at a subsequent June 2013 pediatric visit with Dr. Donoghue. Ex. 6 at 51–53 (reports about B.O.'s speech and propensity for walking on his toes). And Dr. Wooten examined B.O. again on June 24, 2013, for treatment of seizures and Todd's paralysis.[5] Ex. 13 at 62 (also mentioning at this time that B.O. was not talking yet). By August of that year, Dr. Donoghue diagnosed B.O. with developmental delay. Ex. 6 at 48–50.

By the fall of 2013, B.O. was experiencing an increase in seizures, mainly displaying left sided changes of going limp, followed by a left sided Todd's paralysis. Ex. 13 at 57. Treaters assessed him with right hemispheric onset and complex partial secondarily-generalized seizures. *Id*. at 60. It was also noted that B.O. had experienced two breakthrough seizures—without a provoking event like a clear illness or vaccine reaction. *Id.* Additional seizure activity occurred in November and December. Ex. 7 at 14; Ex. 13 at 24–27, 35.

[5] Defined as a "hemiparesis or monoparesis lasting for a few minutes or hours, or occasionally for several days, after an epileptic seizure." *Todd paralysis,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=96185&searchterm=Todd%20paralysis (last visited Aug. 8, 2023).

Medical History Through Time of Claim's Filing

By January 2014 (and after B.O. had experienced a five-minute seizure leading to his hospitalization), treaters were identifying his diagnosis as "genetic epilepsy with focal seizures." Ex. 13 at 10–11. B.O. was seen in early spring by the neurology service at the Children's Hospital of Philadelphia. Ex. 3 at 1–6. The records from that visit indicate that an Athena febrile seizure panel/early infantile epilepsy panel was reported as normal. *Id*. at 3. The impression was that B.O. had epilepsy and autistic features, without identified etiology. *Id*. at 5. The neurologists at Children's Hospital noted that B.O. "seizes so frequently that while he appears to have a developmental delay, he may be intermittently encephalopathic due to the frequency of his seizures." *Id*.

At an April 10, 2014 visit with pediatric neurologist Roha Khalid, M.D., B.O. was noted to be having staring spells, including behavioral arrest for about ten seconds, with his eyes half closed. Ex. 17 at 74–75. These episodes occurred approximately ten times per day. *Id*. B.O. was also displaying fine motor and speech delay, and was receiving services for these issues. *Id*. B.O. was admitted overnight at Duke for an EEG and MRI with sedation on April 29, 2014. Ex. 10 at 293; Ex 17 at 176. The MRI showed asymmetric hippocampi, larger on the left with subtle loss of normal internal architecture, but normal signal intensity. Ex. 10 at 293; Ex 17 at 176. Based on B.O.'s lactate levels, Dr. Mikati called B.O.'s father about the results and stated that B.O needed to be evaluated by genetic specialists for a metabolic disorder. Ex. 10 at 282.

B.O. presented again to Dr. Mikati on August 7, 2014. Ex. 10 at 340–44. B.O.'s mother now reported that he was having more than 100 episodes of absence seizures per day. *Id*. at 341. He was later seen by Dr. Mikati again that fall, where video monitoring was performed to determine if B.O. fulfilled the criteria of Lennox Gastaut Syndrome.[6] *Id*. at 353–56. On October 28, 2014, B.O.'s family met with a physician's assistant at the Department of Neurosurgery at Duke. *Id*. at 357–60. The problem list included Lennox Gastaut Syndrome. *Id*.

Genetic Testing

Initial testing of B.O. did not corroborate a genetic basis for his condition. For example, on September 21, 2016, B.O. was examined by Nurse Practitioner Lori Haskins at Duke. Ex. 38 at 483. B.O.'s patient history noted that a febrile seizure panel performed on March 18, 2014, had been negative for SCN1A and SCN1B mutation. *Id*.; Ex. 3 at 3. A mitochondrial gene panel nuclear

[6] Lennox Syndrome is "an atypical form of absence epilepsy characterized by diffuse slow spike waves, often with atonic, tonic, or clonic seizures and intellectual disability; there may also be other neurologic abnormalities or multiple seizure types." *Lennox Syndrome,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=110889 (last visited Aug. 8, 2023).

and mito normal WES (whole exome sequencing) testing also yielded normal results. Ex. 3 at 3; Ex. 38 at 512.

Later testing, however, resulted in different findings, pointing in the direction of an underlying genetic cause for B.O.'s condition. Based on a treater request, an exome reanalysis was obtained from the lab "GeneDx" on September 13, 2017, with results communicated to the family by genetic counselor Ms. Danielle Hays Karlowicz. Ex. 38 at 997; *see also* Ex. 40 at 61 (GeneDx Genetic Testing Report, dated September 5, 2017). One variant seen in the ARHGEF15 gene was deemed of uncertain significance ("VUS") and reclassified as likely benign, while a variant observed in the CADM1 gene was again classified as VUS. *Id*. However, B.O. was also found, for the first time, to possess a *de novo* heterozygous variant (c. 3551 12_3551_11delCAinsGC). of uncertain significance in the SCN1A gene, but having the possibility of impacting splicing. Ex. 40 at 61–63. The interpretation notes specific to this SCN1A-related finding state as follows:

> The SCN1A gene encodes the alpha subunit of a neuronal voltage-gated sodium channel that regulates the excitability of neurons (Miller et al., 20 I 4). Pathogenic variants in SCN1A cause a variety of epilepsy phenotypes, ranging from simple febrile seizures (FS) to severe infantile epileptic encephalopathies. The most common phenotypes include severe myoclonic epilepsy of infancy (Dravet syndrome), generalized epilepsy with febrile seizures plus (GEFS+), intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTCS), cryptogenic generalized or focal epilepsy, myoclonic-astatic epilepsy, and Lennox-Gastaut syndrome (Miller et al., 2014; Gambardella et al., 2009; Harkin et al., 2007). . . . SCNlA variants are inherited in an autosomal dominant manner and may cause different clinical presentations, even within the same family. Some individuals never develop seizures, indicating incomplete penetrance (Ottman et al., 2010). . . . *Most patients with epileptic encephalopathy harbor a de novo SCNlA pathogenic variant,* . . . .

Id. at 62 (emphasis added). The GeneDx report added the qualification that the variant had not been reported to be benign *or* pathogenic. *Id.* at 63. It also includes the recommendation that additional testing might be warranted "to determine or confirm [B.O.'s] underlying cause of disease," given the uncertainty about the variant's impact (even though the same report acknowledges the association generally between SCN1A mutations and epileptic disorders). *Id.* at 65.

There was a follow-up call on September 18, 2017, between Mrs. Osenbach and Ms. Karlowicz. Ex. 38 at 1004. At this time, Ms. Karlowicz relayed that she had communicated with "a GC at GeneDx who reports that the variant is not in the general population database, there is no information in ClinVar, and it's an inframe variant." *Id*. It was further noted that B.O.'s variant

was *de novo* (meaning not inherited from either parent). *Id*. The variant was listed as occurring in intron 17 at 12 base pairs. *Id*.

On December 1, 2017, B.O. underwent additional genetic testing—a karyotype analysis to examine for ring chromosome 20 mosaicism. Ex. 38 at 1096. Although the note was difficult to read, it suggested that B.O.'s karyotype tested forty-six XY chromosomes, without evidence of any mosaicism. *Id*.

Almost a year later, on October 23, 2018, the Undiagnosed Disease Network ("UDN") at Duke University notified Dr. Mikati that B.O. would not be accepted for evaluation in the program. Ex. 38 at 1597. The principal investigator and a clinical geneticist, Vandana Shashi, M.D., noted that after an extensive review of his medical records plus the pertinent literature, the members of the UDN clinical site were of the opinion that the *de novo* variant in the SCN1A gene was likely causal of B.O.'s clinical presentation. *Id*. While Dr. Shashi recognized that testing had identified the variant to be of uncertain significance, the Duke UDN had obtained additional information on the variant through its in-house bioinformatician.[7] *Id*. Although the variant had not been reported as disease-causing previously, it was absent in control databases, and was predicted to affect splicing. *Id*. In addition, Dr. Shashi noted that pathogenic variants in SCN1A often result in a phenotype consistent with B.O.'s phenotype (thus offering some indirect evidence that the variant could be pathogenic). *Id*. Dr. Shashi added that the goal of Duke UDN was to evaluate patients who do not yet have an answer—whereas there existed a credible explanation for B.O.'s condition. *Id*. These findings were subsequently incorporated into B.O.'s epilepsy care, and the presence of Dravet syndrome was noted in the context of a subsequent November 8, 2018 appointment. *Id.* at 1602–08.

On October 14, 2020, B.O. had another doctor's visit. Ex. 38 at 2428. The notes for the visit indicate the family wanted to wean B.O. off some of his medications deemed ineffective, in favor of others. *Id*. B.O.'s listed diagnoses (again) included Dravet syndrome due to SCN1A mutation, plus generalized tonic-clonic seizures, partial symptomatic epilepsy with complex partial seizures, intractable, with status epilepticus; typical absence seizures; atypical absence seizures; spells of abnormal behavior with flushing increased HR apparent distress and no altered consciousness confirmed right temporal seizures. *Id*.

[7] A person who works with "the organization and use of biological information, particularly computer-driven storage, processing, and analysis of data and databases in the fields of molecular biology and genetics." *Bioinformatics,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=6209&searchterm=bioinformatics (last visited Aug. 8, 2023).

II. Expert Testimony and Reports

A. *Petitioners' Testifying Expert – Mahbubul Huq, M.B.B.S., Ph.D.*

Dr. Huq, a pediatric neurologist, submitted two written expert reports and testified for Petitioners. See generally Tr. at 5–87, 158–166. Report, dated Feb. 6, 2017, filed as Ex. 36 (ECF No. 43-1) ("Huq First Rep."); Report, dated Dec. 1, 2021, filed as Ex. 39 (ECF No. 82-1) ("Huq Second Rep."). Dr. Huq opined that the vaccinations B.O. received could have worsened his existing seizure disorder, proposing a medical theory to support his contentions.

Dr. Huq attended Dhaka Medical College in Bangladesh for his medical degree and Tokushima University School of Medicine for his doctorate degree in medical science. Tr. at 5; Curriculum Vitae, dated Feb. 6, 2017, filed as Ex. 37 (ECF No. 43-2) ("Huq CV") at 1. He then completed a residency in pediatrics, neurology, and clinical genetics at Wayne State University and Baylor College of Medicine, and later post-doctoral fellowships in genetics at Baylor College of Medicine and the University of British Columbia. Tr. at 5; Huq CV at 1. He is a clinical geneticist at Children's Hospital of Michigan and a Professor of Pediatrics and Neurology at Wayne State University. Tr. at 6–7; Huq CV at 1. He has treated thousands of patients with epilepsy and developmental delay. Tr. at 7; Huq First Rep. at 1. He has also published peer-reviewed articles on the genetics of epilepsy and neurodevelopmental disorders. Tr. at 7; Huq First Rep. at 1. He is board certified by the American Board of Psychiatry and Neurology and the American Board of Medical Genetics. Tr. at 5–6; Huq CV at 2.

Dr. Huq first discussed status epilepticus generally.[8] In his view, not all seizures or seizure series have the same impact; sometimes a long seizure does not lead to additional deficits, whereas a short seizure may cause significant neurologic damage. Tr. at 11, 63. This distinction, he proposed, could have something to do with a seizure's underlying cause, noting that more damage is likely where a seizure has an acute symptomatic cause (e.g., hypoxia, meningitis, encephalitis, or severe trauma to the head). *Id*. at 11. He also observed that there is always some variable age-related susceptibility, although the impact of that factor is less understood. *Id*. at 11–12, 14, 63. In Dravet syndrome (which is seen in children born with a sodium channel genetic mutation), seizures typically only begin at four to six months of age, for reasons that cannot be fully ascertained based on existing science. *Id*. at 14.

[8] Status epilepticus refers to "a prolonged series of seizures without return to full consciousness between them; the two major types are *convulsive s. epilepticus,* which is life-threatening, and *nonconvulsive s. epilepticus,* which is serious but not usually life-threatening. *Status Epilepticus,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=108327&searchterm=status+epilepticus (last visited Aug. 8, 2023).

Dr. Huq next turned to B.O.'s history. B.O. was born healthy, with no concerns about development in his first months of life. Tr. at 8; Huq First Rep. at 2. He received vaccinations at two and four months, but at his four-month vaccination he developed a hyperresponsive state with weakness on one side of the body that could have been a seizure. Tr. at 8; Huq First Rep. at 2. He had two more episodes later that year, but otherwise continued to meet all his developmental milestones and have normal examinations. Tr. at 8.

This pre-vaccination history, in Dr. Huq's view, was distinguishable from what came after. B.O. received the vaccines at issue in April 2013, when he was approximately 13 months old. Tr. at 8; Huq First Rep. at 2. Within 24 hours, B.O. experienced a belatedly prolonged seizure that lasted approximately 30 minutes. Tr. at 9–10, 12; Huq First Rep. at 2–3; Ex. 7 at 1. That seizure was accompanied by significant hypoxia,[9] and B.O. became apneic within approximately 8-13 minutes. Tr. at 9–10, 12; Huq First Rep. at 1; Huq Second Rep. at 5; Ex. 7 at 1. When he was admitted to the hospital he had an abnormal EEG with right sided slowing, although his brain MRI was normal. Huq First Rep. at 1. A month after that, even though B.O.'s physical examination was fine, his vocalization was deemed absent. Tr. at 9, 15–16; Ex. 17 at 21–22. The next month in June, (now two months after vaccination), B.O.'s pediatric neurologist noted that he had only said two words, and he was concerned about his language development. Tr. at 9, 18–19; Huq First Rep. at 3; Ex. 6 at 51; Ex. 13 at 63, 65. And by August (four months after vaccination), B.O. was officially deemed to be developmentally delayed, necessitating his participation in an early developmental intervention program.[10] Tr. at 9, 19–20, 21–22; Ex. 2 at 9; Ex. 6 at 48; Huq First Rep. at 3.

Dr. Huq acknowledged the existence of B.O.'s genetic mutation in the SCN1A gene. Tr. at 35; Huq Second Rep. at 2. Indeed, even before B.O.'s fourth seizure, whole exome sequencing in 2014 had identified the existence of variants[11] of unknown clinical significance in other genes (the ARHGEF15 and CADM1 genes). Tr. at 35–36; Huq Second Rep. at 2. But Mrs. Osenbach had both of these variants as well, so in his view their genetic impact was likely benign, since she was otherwise healthy. Huq Second Rep. at 2. A second round of such testing, however, revealed the existence of a variant of unknown significance in the SCN1A gene. *Id.*; Tr. at 36–39, 42–43;

[9] Dr. Huq defined hypoxia as a lack of oxygen than can lead to brain damage. Tr. at 12–13.

[10] The purpose of an early developmental intervention program, according to Dr. Huq, is to identify developmental issues and neurodevelopmental conditions to provide treatments and therapies to minimize any disability. Tr. at 21–22.

[11] As Dr. Huq explained, laboratory testing includes five categories of genetic variants. Tr. at 37. First, there is the benign variant, which presents in healthy individuals but with no unexpected or malign effect. *Id.* Next is a pathogenic variant, which when identified reflects the view that the variant (to a 100 percent certainty) is disease-causing. *Id.* Third are variants deemed "likely pathogenic," in which case the variant is thought to be causal of disease but without certainty. *Id.* The fourth category is "likely benign," the variant is more likely than not benign. *Id.* at 37–38. Finally, the last category is a variant of uncertain significance, in which case the variant's effect cannot be identified either way. *Id.* at 38. Here, there was an absence of functional studies done on this variant to determine whether it was pathogenic or benign. Tr. at 39–42.

Huq First Rep. at 2; Ex. 40 at 61, 63. That particular variant has never been seen in any other epilepsy patient or in any healthy person. Tr. at 36, 38, 42; Huq Second Rep. at 2. Dr. Huq did not dispute that it might affect splicing. Tr. at 36, 38. (Typically, a gene codes for the production of RNA, which in turn "makes" the protein specific to it. *Id.* at 36. A splicing variant can cause errors in the proteins made from the incomplete RNA). *Id.*

The Duke UDN had classified this SCN1A variant as likely causal of B.O.'s clinical condition. Tr. at 36–39, 42–43; Huq First Rep. at 2; Huq Second Rep. at 2; Ex. 40 at 61, 63. But Dr. Huq deemed the UDN's determination to be arbitrary, since the exome sequencing in the second round of testing relied on the same information and material as the first (which had not reached the same conclusions). Tr. at 64–65; Huq Second Rep. at 2. Indeed, in his view, because B.O. was the only epilepsy patient possessing this variant, it was particularly speculative to characterize it as likely pathogenic. Tr. at 64–65; Huq Second Rep. at 2, 8.

In fact, Dr. Huq emphasized, even a demonstrated pathogenic mutation in SCN1A is not always sufficient to cause intractable epilepsy. Huq Second Rep. at 2. In support of this contention, he referenced one study that looked at how inaccurate and unreliable the reporting of different sodium channel mutations was with computer analysis alone, noting that experimental functional studies were ultimately necessary to more definitively deem a particular genetic variant to be pathogenic. Tr. at 43, 45; Huq Second Rep. at 5; D. Lal et al., *Evaluation of Presumably Disease Causing SCN1A Variants in a Cohort of Common Epilepsy Syndromes*, PLoS One 1, 2, 10 (2016), filed as Ex. 39, Tab BB (ECF No. 89-7) ("Lal").[12] Of 448 epilepsy patients and 750 healthy control individuals considered in Lal, only eight possessed a sodium channel mutation (underscoring the baseline fact that as a general rule, not all epilepsy patients have the mutation, while some individuals not suffering from epilepsy do). Tr. at 43–44, 48; Lal at 4–5, 9. Further analysis in Lal revealed that seven of these subject patients had *benign* variants, with the single one deemed pathogenic proving not to be associated with damaging clinical symptoms. Tr. at 44–46; Lal at 10. Thus, B.O.'s variant could not be assumed pathogenic simply on the basis of his negative clinical presentation. Tr. at 45.

In addition, Dr. Huq noted that sodium channel variants akin to B.O.'s genetic variant are found in many SCN1A-related disorders running a spectrum of severity—including febrile epilepsy, Dravet syndrome, and intractable focal generalized seizure (common epilepsy). Tr. at 48–50. But in Dr. Huq's view, the current consensus on the role of the sodium channel variant in the SCN1A gene is that it functions as a risk allele—meaning it may increase the risk of epilepsy (just as cholesterol or smoking increase the risk of a stroke), but does not *cause* a seizure disorder by itself. *Id.* at 49, 60. He also noted the genotype/phenotype correlation is poor given the variable expressivity of SCN1A disorders, adding that other factors (including the environment) ultimately

[12] Also filed as Respondent's Ex. B, Tab 19.

into the severity of the injury. *Id.* at 51–53; Huq Second Rep. at 3; D. Mei et al., *Dravet Syndrome as Part of the Clinical and Genetic Spectrum of Sodium Channel Epilepsies and Encephalopathies*, 60 Epilepsia S2, S2 (2019), filed as Ex. 39, Tab GG (ECF No. 90-5).

Nevertheless, Dr. Huq agreed that the diagnosis for B.O.'s specific neurological disorder reasonably included Dravet syndrome in the differential, along with other conditions like Lennox Gastaut syndrome (as the record revealed had been suspected by treaters) or epileptic encephalopathy. Tr. at 65–66, 69, 84–85; Huq First Rep. at 1. He agreed that Dravet syndrome can be clinically diagnosed, and in this case (especially after the genetic testing results from Duke UDN) B.O.'s treaters had at times embraced such a diagnosis. Tr. at 66, 84–85. However, he also noted that a Dravet syndrome patient would not usually receive the kind of sodium channel drugs some treaters had used for B.O., since there was a consensus among neurologists that they were to be avoided. *Id*. at 161–64. Such record evidence actually suggested to Dr. Huq that B.O.'s treaters most likely believed he was suffering from an epileptic encephalopathy of unknown cause. *Id*. at 162. Dr. Huq did not include autoimmune epilepsy within his differential diagnoses for B.O. *Id*. at 85–86.

The other side of Dr. Huq's testimony and expert reports involved the putative role that the two vaccines B.O. had received in April 2013 could have played in worsening his seizure disorder/epilepsy. Vaccines, he observed, by their very function generate an immune response. Tr. at 25; Huq First Rep. at 7; Huq Second Rep. at 6–7. In particular, vaccines are designed to provoke adaptive immunity in response to their specific antigenic components, doing so by causing immediate localized inflammation at the vaccine site that can often lead to pain or swelling. Tr. at 23. But vaccine-induced inflammation can also have distant organ effects. *Id.* at 23–25; Huq Second Rep. at 6; C. Hervé et al., *The How's and What's of Vaccine Reactogenicity*, 39 Nat. Partner J.'s 1, 3–4 (2019), filed as Ex. 39, Tab V (ECF No. 89-1) ("Hervé") at 3–4 (demonstrating the local and distant organ effect derived from vaccination).

The intentionally immune-stimulating impact of a vaccine could in turn also impact neurologic processes relating to seizures, even though the seizure activity would not itself occur at the vaccine's situs. K. Riazi et al., *Contributions of Peripheral Inflammation to Seizure Susceptibility: Cytokines and Brain Excitability*, 89 Epilepsy Res. 34, 38 (2009), filed as Ex. 36, Tab KK (ECF No. 51-8) ("Riazi"). Thus, vaccine antigens binding to pattern recognition molecules would be recognized as foreign by pattern recognition receptors in the body, and thereafter activated local immune cells would recruit other cells like leukocytes and lymphocytes, which secrete chemokines and cytokines. Tr. at 25, 33–34. These messenger chemicals activate T and B lymphocytes that make it possible to generate antibodies and T-cell responses. *Id*. at 25–26. As they travel through the body, the cytokines produced in response to vaccination can theoretically harm endothelial cells of the brain sufficient to breach a physical/cellular barrier protecting the brain. *Id.* at 26, 33. Such cytokines pass through the barrier, stimulating glial cells,

producing localized inflammation, and allowing the entry of even larger immune molecules into the brain to create localized inflammation or cause increased excitability. *Id.* at 26, 33–34, 60; Huq First Rep. at 3; Huq Second Rep. at 1, 5–6.[13]

In this way, Dr. Huq opined, vaccines could trigger seizures as a result of the inflammation they promote, which he distinguished in effect from other kinds of physical trauma or stress that could also spark seizures). Tr. at 23, 87; Huq Second Rep. at 5–7. Although the human immune response process is usually well controlled, with the effect of cytokines short-lasting, a vaccine (in concert with individual or other environmental factors) could trigger seizure in a vulnerable child. Tr. at 27–30, 35, 163; Huq Second Rep. at 4; A. Vezzani et al., *The Role of Inflammation in Epilepsy*, 7 Nat. Rev.'s Neurology 1, 23–24 (2011), filed as Ex. 36, Tab YY (ECF No. 50-2) ("Vezzani").

A number of studies and other evidence confirmed this possibility, Dr. Huq maintained. Tr. at 30; Hervé at 39. For example, it is known that some inflammatory conditions or diseases (e.g., encephalitis, meningitis, and autoimmune epilepsy) are associated with an increased seizure risk. Tr. at 31–32. Though the mechanism by which these conditions occur is not well studied, immune therapies that help control inflammation can also ameliorate seizure activity. *Id.* at 32. In another study, scientists collected peripheral blood mononuclear cells from children with Dravet syndrome (who also possessed an SCN1A mutation) and exposed them to vaccine components, revealing that the vaccine exposure resulted in a more pronounced inflammatory response. *Id.* at 60–62, 78–81; Huq Second Rep. at 3–5; S. Auvin et al., *Altered Vaccine-Induced Immunity in Children with Dravet Syndrome*, 59 Epilepsia e45 (2018), filed as Ex. 39, Tab D (ECF No. 86-4) ("Auvin").[14]

On cross examination, Dr. Huq expressed unawareness of the fact that Auvin's authors had *also* concluded that the precipitation of seizure onset due to vaccination did not also affect the subsequent course of the disease. Tr. at 73; Auvin at e45 ("precipitation of seizure onset by immunization does not affect the course of the disease"), e49. He otherwise admitted to the existence of studies suggesting that even if vaccines are implicated in an earlier onset of seizures in Dravet syndrome patients, such seizures do not alter the course of the disease, but maintained that the studies were flawed (either because they were small, retrospective, or lacking in randomization and matched case control design). Tr. at 74–76, 159, 164–65; Huq Second Rep. at 4; N. Verbeek et al., *Effect of Vaccinations on Seizure Risk and Disease Course in Dravet Syndrome*, 85 Neurology 596, 601–02 (2015), filed as Ex. 39, Tab VV (ECF No. 92-7) ("Verbeek

[13] In his expert reports, Dr. Huq also discussed the potential role of the adjuvant contained in the pneumococcal vaccine to disrupt the blood/brain barrier and cause inflammation. Huq First Rep. at 4. But he did not address it during his testimony, or in Petitioners' redirect case in response to Dr. Raymond's criticisms.

[14] Also filed as Respondent's Ex. B, Tab 36.

I"); A. McIntosh et al., *Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study*, 9 Lancet Neurology 592, 597 (2010), filed as Ex. 39, Tab FF (ECF No. 90-4) ("McIntosh") (acknowledging that a limitation of the study was a design that prevented the evaluation or discussion of gene environmental interaction or interactions of the vaccine and sodium channel mutation).[15] However, McIntosh also found that children with SCN1A mutations should still receive vaccinations, since there was no evidence that vaccinations before or after disease onset affect the outcome. McIntosh at 597.

In contrast, Dr. Huq referenced two studies discussing the interaction of possible environmental and genetic factors in the context of SCN1A mutation Dravet syndrome. Tr. at 53–63, 160; L. Deng et al., *Vaccination Management in an Asymptomatic Child with a Novel SCN1A Variant and Family History of Status Epilepticus Following Vaccination: A Case Report on a Potential New Direction in Personalised Medicine*, 78 Seizure 49, 49 (2020), filed as Ex. 39, Tab K (ECF No. 87-4) ("Deng");[16] A.R. Salgueiro-Pereira et al., *A Two-Hit Story: Seizures and Genetic Mutation Interaction Sets Phenotype Severity in SCN1A Epilepsies*, 125 Neurobiology Disease 31, 31 (2019), filed as Ex. 39, Tab JJ (ECF No. 97-3) ("Salgueiro-Pereira").[17]

Deng is a case report regarding two siblings—one of whom had a sodium channel variant and developed prolonged seizures to the point of cardiac arrest and expiration. Tr. at 53; Deng at 50. The other sibling was hospitalized and monitored due to his family history (without knowing whether he had the same sodium channel variant), but had a good outcome with aggressive controlled treatment, after receiving a vaccination. Tr. at 53; Deng at 50–51. In Dr. Huq's reading, Deng established the possibility of modifying phenotypes of sodium channel deficiencies (despite its exceedingly small, "n of two" sample size). Tr. at 53–54; Deng at 51. Salgueiro-Pereira used genetically-altered mice to evaluate a mutation known to cause generalized febrile seizures,[18] and in rare circumstances Dravet syndrome. Tr. at 56; Salgueiro-Pereira at 32. Its authors induced seizures in the studied mice via chemicals, while also conducting the same experiment to control for mice that did not possess the mutation but were otherwise genetically homogeneous. Tr. at 56; Salgueiro-Pereira at 32. The mutated mice exposed to early seizures had a more severe phenotype and more frequent, spontaneous seizure, as well as behavioral deficits. Tr. at 57; Salgueiro-Pereira at 41. This result suggested, in Dr. Huq's opinion, that the environmental factor was the key to severity—not genetics per se, as Respondent was arguing. Tr. at 57–59, 161, 165–66.

[15] Also filed as Respondent's Ex. B, Tab 28.

[16] Also filed as Respondent's Ex. B, Tab 35.

[17] Also filed as Respondent's Ex. B, Tab 23.

[18] This mutation reflects an SCN1A-type model in humans. Tr. at 58.

Dr. Huq also opined that his theory—that B.O.'s receipt of the pneumococcal and IPV vaccines[19] aggravated his underlying seizure disorder and adversely affected his development—had record support. Tr. at 22–23, 63–64; Huq First Rep. at 3; Huq Second Rep. at 6, 9. He did not question the fact that B.O. had experienced two to three possible seizures *prior* to April 2013, and that several of these did not occur in the context of vaccination (even though B.O. did receive vaccines in this intervening period). Tr. at 9, 13, 76. But no matter to what extent these earlier seizures might have contributed to his neurological disorder, they were, in Dr. Huq's opinion, less damaging than what occurred after the April 2013 vaccinations. *Id*. at 9, 13, 67–68, 76; Huq Second Rep. at 1, 6. B.O. thereafter not only developed more frequent, and intractable, seizures but also displayed severe developmental limitations and deficiencies. Tr. at 9–10, 13, 15. No developmental concerns were expressed prior to this time. *Id*. at 22, 68, 84; Ex. 13 at 72. And Dr. Huq rejected attributing these changes to a developmental brain anomaly or genetic mutation, since B.O. has had numerous neurological evaluations and extensive genetic testing, but with no definite disease-causing mutation that can explain his condition. Huq First Rep. at 8. (This argument, of course, ignores the Duke UDN determination that deemed B.O.'s SCN1A mutation as explanatory).

In addition, Dr. Huq deemed significant the fact that B.O.'s treaters had not only earlier proposed that his initial seizures were vaccine-related, but had discussed the need to prophylactically treat B.O. with anti-seizure medication in anticipation of vaccination, thus revealing the implicit view of a vaccine-seizure association. Tr. at 82–84; Ex. 13 at 70. By contrast, he downplayed the fact that B.O.'s MRI in April 2014 did not confirm his theory (for example, by revealing blood-brain barrier changes). Ex. 10 at 293; Ex 17 at 176. In Dr. Huq's view, such changes might be too subtle to pick up via this kind of imaging. Tr. at 77–78. He similarly deemed the fact that the MRI also did not show any signs of abnormalities as insignificant, since MRIs do not show all types of neurological injury. *Id.* at 78.

Finally, Dr. Huq briefly discussed the timeframe in which B.O. experienced his post-vaccination injury, deeming it medically acceptable and consistent with the proposed mechanism of inflammation, blood brain barrier disruption, and release of cytokines by vaccination. Huq First Rep. at 7. Seizures occurring a day after vaccination reflected a medically-acceptable timeframe for an innate immune-mediated process involving inflammation encouraged by cytokines. *Id.*

B. *Respondent's Testifying Expert – Gerald Raymond, M.D.*

Dr. Raymond, a clinical geneticist, testified on behalf of Respondent and submitted one expert report. *See generally* Tr. at 89–158; Report, dated Jan. 31, 2022, filed as Ex. B (ECF No.

[19] Dr. Huq ultimately deemed both to be potentially causal, even though there is some discussion in Dr. Huq's expert reports about the pneumococcal vaccine specifically. Tr. at 86–87; Huq First Rep. at 3–4.

95-1) ("Raymond Rep."). Dr. Raymond opined that B.O.'s disease presentation and clinical condition was not likely caused or exacerbated by the vaccines he received in April 2013.

Dr. Raymond attended Fairfield University for his undergraduate degree, and the University of Connecticut School of Medicine for his medical degree. Tr. at 89; Curriculum Vitae, dated July 26, 2022, filed as Ex. C (ECF No. 106-1) ("Raymond CV") at 1; Raymond Rep. at 1. He then did a residency in pediatrics at Johns Hopkins followed by a three-year residency in neurology at Massachusetts General Hospital. Tr. at 89–90; Raymond CV at 1; Raymond Rep. at 1. Dr. Raymond also completed fellowships at the Université Catholique do Louvain in Brussels specializing in developmental neuropathology, Massachusetts General Hospital specializing in pediatrics and genetics and teratology, and Harvard Medical School specializing in neurology. Tr. at 90; Raymond CV at 1; Raymond Rep. at 1–2. He is currently employed at Johns Hopkins University Hospital, where he is a professor of genetic medicine and neurology. Tr. at 90; Raymond CV at 3; Raymond Rep. at 1. Dr. Raymond has published numerous peer-reviewed articles in pediatric neurology and clinical genetics and has treated over a thousand patients with a seizure disorder in the past five years. Tr. at 91; Raymond CV at 3–11; Raymond Rep. at 1. He is board certified in neurology, with special qualifications in child neurology as well as clinical genetics, and is licensed to practice medicine in Maryland. Tr. at 90; Raymond CV at 18; Raymond Rep. at 1.

Dr. Raymond began by discussing Dravet syndrome, which he defined to be early infantile encephalopathy. Tr. at 92; Raymond Rep. at 7. Dravet syndrome typically begins in the first year of life in children who are otherwise developing normally, presenting with initial seizures between four to eight months of age. Tr. at 92–93; Raymond Rep. at 7. The seizures are typically tonic-clonic,[20] although they may only manifest in one part of the body. Tr. at 93. These first events are often associated with (if not directly triggered by) fever, and temperature sensitivity stays with those individuals throughout their life. *Id.* at 93; Raymond Rep. at 7. After about their second year of life, children with Dravet syndrome experience developmental plateauing, and such individuals demonstrate intellectual disability, ataxia, and sleep disturbances. Tr. at 93. Seizures are also a characteristic of Dravet, and although they often present initially as tonic-clonic, they can become more mixed, and are classically refractory. *Id.* at 93; Raymond Rep. at 7. Children with Dravet syndrome do not respond well to anti-seizure medication. Tr. at 93.

Dravet syndrome is clinically diagnosed. Tr. at 93; Raymond Rep. at 24. Many individuals with Dravet syndrome also are found to possess variants in the SCN1A gene, which is responsible for the production of voltage-gated sodium channels in the brain that in turn play a role in nerve signal transmission. Tr. at 93; Raymond Rep. at 9, 24. Other genes have also been implicated in

[20] Tonic-clonic, also known as tonicoclonic, is defined as "both tonic and clonic; said of a spasm or seizure consisting of a convulsive twitching of the muscles." *Tonicoclonic,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=50263 (last visited Aug. 8, 2023).

Dravet syndrome, however, and the medical community has not reached consensus as to whether an SCN1A mutation *alone* will result in Dravet syndrome, or if other genes are also implicated. Tr. at 94; Raymond Rep. at 8.

A variety of literature pertaining to Dravet syndrome highlights the role of genetic modifiers (specifically the degree of genotype/phenotype correlation with SCN1A gene variants) in clinical severity. Tr. at 119–20. There is generally a spectrum[21] of epilepsy/seizure disorder-related phenotypes, from self-limited febrile seizures on the mild side to full-blown cases of Dravet syndrome on the more severe side.[22] *Id.* at 120–21, 133–34; Raymond Rep. at 9, 16. Persons with an SCN1A variant or mutation can even be wholly asymptomatic. Tr. at 121. At most, certain variants (truncated mutations, complete gene deletions, exon deletions, and frame shifts) are associated with a more severe phenotype. *Id.* at 120, 132–33; Raymond Rep. at 11, 17; C. Marini et al., *The Genetics of Dravet Syndrome*, 52 Epilepsia 24, 24–26 (2011), filed as Ex. B, Tab 17 (ECF No. 96-7) ("Marini"); *see also* V. Cetica et al., *Clinical and Genetic Factors Predicting Dravet Syndrome in Infants with SCN1A Mutations*, 88 Neurology 1037, 1037–038 (2017), filed as Ex. B, Tab 22 (ECF No. 97-2) (highlighting the need to clarify with further research whether the worst prognosis related to a younger age at seizure onset can be entirely explained by genetic factors).

Dr. Raymond nevertheless maintained that most instances of Dravet syndrome involve a predictably severe outcome, with some variation always possible depending on the individual. Tr. at 136. Infants experiencing Dravet would this be expected to experience worsening, as the defective SCN1A gene's role in causing dysfunction in voltage-gated sodium channels progressed in tandem with a child's brain development, although earlier onset of the problem would likely impact how damaging the process became over time. *Id.* at 133, 136–37; Marini at 26 (discussing phenotypic variability such as age of seizure onset). Based on the record in this case, Dr. Raymond opined, B.O.'s mutation was more likely to have been on the more damaging/severe end of the spectrum in light of his demonstrated clinical course, although he agreed that he could not match the variant to some of the known mutations associated with severe outcomes. Tr. at 133, 142; Raymond Rep. at 17.

Environmental factors, by contrast, were not likely in Dr. Raymond's opinion to play much of a role in affecting the severity of a course of Dravet syndrome. Tr. at 113–14, 122–24; Raymond

[21] Raymond Rep. at 16; S. Kivity et al., *SCN1A Clinical Spectrum Includes the Self-Limited Focal Epilepsies of Childhood*, 131 Epilepsy Res. 9, 10 (2017), filed as Ex. B, Tab 21 (ECF No. 97-1).

[22] Dr. Raymond noted more specifically that many scientific articles have begun to demonstrate that some kinds of variants (truncation mutations or those causing loss of function) the correlation with the severity of disease is better demonstrated. Tr. at 120. He stated that it is difficult with the missense variants to just simply look at their placement or their amino acid variants, but there is an increasing role for the demonstration that the genotype can demonstrate what kind of disease severity you are going to have. Tr. at 120.

Rep. at 18; *see* A. Escayg & A. Goldin, *Sodium Channel SCN1A and Epilepsy: Mutations and Mechanisms*, 51 Epilepsia 1650, 1653, 1656 (2010), filed as Ex. B, Tab 11 (ECF No. 96-1) ("Escayg") (finding that the expression of the mutation in transmitting parents was modified by genetic factors, and thus the severity of the variant in their offspring reflects the full expression of the affected gene).

However, some of Respondent's articles seemed to admit the possibility of a greater impact by environmental factors, as noted in Petitioners' cross-examination of Dr. Raymond. For example, one article states there might be a spectrum where genetics *and* environmental factors interact via ion channels. S. Berkovic et al., *Human Epilepsies: Interaction of Genetica and Acquired Factors*, 29 Trends Neurosciences 391, 394–96 (2006), filed as Ex. B, Tab 27 (ECF No. 97-7) ("Berkovic"). Other items of literature expressed a similar view. *See, e.g.*, A. Tukker et al., *The Impact of Environmental Factors on Monogenic Mendelian Diseases*, 181 Toxicological Sci.'s 3, 6 (2021), filed as Ex. B, Tab 18 (ECF No. 96-8) (indicating that environmental and genetic factors interact to modify variable expressivity, progression, severity, and onset but *not* discussing vaccines as an environmental factor); J. Mulley et al., *SCN1A Mutations and Epilepsy*, 25 Hum. Mutation 535, 538 (2005), filed as Ex. B, Tab 8 (ECF No. 95-9) (indicating patients with the same gene can display different phenotypes). But Dr. Raymond maintained these determinations all constituted unsubstantiated hypotheses, and that it was simplistic to give environmental factors too much causal weight, given the lack of empirical evidence supporting the contention otherwise. Tr. at 114–19, 130–32, 134–36; Raymond Rep. at 14–15.

Dr. Raymond then reviewed the medical records bearing on B.O.'s diagnosis, opining that his clinical trajectory, symptoms, and testing results were collectively consistent with Dravet syndrome. Tr. at 94, 112, 152. B.O. had first presented with seizures when he was about four months old, with the first such seizure probably associated with a fever following the July 2012 vaccination. *Id.* at 94, 152; Raymond Rep. at 24. B.O. then experienced two other events associated with fever, and then (when he was approximately a year and a half old) he began to experience afebrile events. Tr. at 94. His developmental issues now also manifested more clearly. *Id*. at 94–95, 148–49. B.O. has had significant language delay, and continues to suffer from refractory seizures of several different types (partial as well as generalized tonic-clonic), and many events of status epilepticus. *Id.* at 95, 149; Raymond Rep. at 7. He has also been medically refractory and subsequently found to have a variant in his SCN1A gene that is de novo[23] and has been predicted to affect splicing (a conclusion Dr. Raymond found persuasive).[24] Tr. at 95, 97, 124, 127, 152;

[23] Dr. Raymond explained that a de novo variant or mutation is a change in a gene that was not inherited but instead arose spontaneously. Tr. at 95. In Dravet syndrome, most of the genetic variants resulting in a severe form are de novo. *Id*.

[24] Splicing is an important step in the taking of information from DNA, in the process of transcribing and transmitting messenger RNA out to the cell where it gets translated into a protein. Tr. at 96. Interruptions in splicing are common causes of disease. *Id.*

Raymond Rep. at 7, 11, 24; Ex. 40 at 62–63. And B.O.'s course was, in Dr. Raymond's experience, consistent with the experience of other children diagnosed with Dravet syndrome. Tr. at 97–98, 112, 125, 127, 148–49, 154; Raymond Rep. at 24.

Dr. Raymond also addressed the findings of UDN at Duke University and their relevance to B.O.'s proposed Dravet diagnosis. Although Dr. Huq had deemed their interpretation of B.O.'s genetic testing (which essentially determined that B.O.'s SCN1A variant was most likely explanatory of his illness) to be arbitrary, especially in light of GeneDx's classification of the variant as of unknown significance, Dr. Raymond disagreed, arguing that the Duke UDN group had extensive experience with the interpretation of exome sequencing data and correlation with clinical phenotype, and thus its findings were reliable. Raymond Rep. at 22–23. The earlier GeneDx results also could not, in Dr. Raymond's opinion, be read to wholly *reject* the possibility that B.O. possessed a pathogenic variant, adding that they expressly noted that the observed variant *could* affect splicing. Tr. at 125–26; Ex. 38 at 997, 1055, 1179, 1597; Raymond Rep. at 11–12; Ex. 40 at 63. And although articles cited by Dr. Huq, like Lal, seemed to support the contention that SCN1A mutations were commonly mislabeled as pathogenic, Lal's actual findings were more limited in scope. Tr. at 128–30; Raymond Rep. at 15–16; Lal at 2–3 (only seven out of over 1198 patients total deemed to have represented a misclassified mutation).[25] None of the highlighted variants from Lal deemed erroneously identified as pathogenic were found in B.O. in any event. Raymond Rep. at 16.

Ultimately, Dr. Raymond maintained, to a clinical geneticist the precise identification of whether B.O.'s variant had pathologic significance would be less important than the fact that the variant had been discovered *in the context* of B.O.'s overall clinical course and treatment (which was itself phenotypically consistent with Dravet syndrome). Tr. at 96–97, 152–53; Raymond Rep. at 11–12, 22–24. It was simply likely that the discovered SCN1A variant was associated with (and therefore confirmed) B.O.'s Dravet syndrome. Studies sufficient to demonstrate how a variant might impact disease course were in fact extremely difficult to come by, and therefore clinical geneticists must use their best judgment in analyzing the entire clinical situation to make a diagnosis.[26] Tr. at 97, 127–28, 142–43, 152–53. And even if it were certain that B.O.'s mutation

[25] Dr. Raymond contended that Lal obtained the misidentified-as-pathogenic mutations from a large scientific database (which identified "more than 1000 disease-associated mutations for the SCN1A gene"). Raymond Rep. at 15; Tr. at 129; Lal at 3. Once the seven non-pathogenic variants were determined, Lal's authors looked back to the database to determine *why* they had been included there in the first place, finding that disease association was in fact not supported (either because the mutations were not *de novo*, were from older reports, had been one of other clearly-pathogenic mutations identified, etc.). Dr. Raymond thus concluded that the inclusion of these mutations in the database reflected poor "curation" of its contents more than anything else (Tr. at 130)—and regardless, the fact that only a handful had been incorrectly identified as pathogenic out of more than a thousand reflected a foreseeable statistical error, rather than evidence that mutations were *routinely* misclassified, as Dr. Huq proposed. Raymond Rep. at 16.

[26] Dr. Raymond admitted, however, that some literature stands for the proposition that evidence of the existence of a genetic variant of uncertain significance should *not* be used in clinical decision making. Tr. at 143–44; S. Richards et al., *Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the*

was of unknown significance, Dr. Raymond stated, he would still opine that B.O.'s presentation was consistent with Dravet syndrome, albeit with a genetic etiology unknown. *Id.* at 153.

Next, Dr. Raymond criticized Dr. Huq's medical theory. As he understood it, Dr. Huq was disregarding the likely impact of the SCN1A mutation in favor of vaccination as a trigger for an inflammatory reaction that released cytokines both locally and systemically, leading to opening of the blood-brain barrier and subsequent brain function alterations which resulted in seizures, developmental delays, and other issues.[27] Tr. at 98; Raymond Rep. at 12. But Dr. Raymond maintained that literature relied upon by Dr. Huq for this proposition (and more broadly for the idea that external environmental factors like vaccines could impact Dravet syndrome course meaningfully, as opposed to in a transient manner) was inapplicable or unpersuasive. Tr. at 101–12; Raymond Rep. at 17–18.

Salgueiro-Pereira, for example, involved a mutation distinguishable from what B.O. likely possessed. Tr. at 101–03. Indeed, that study's authors had genetically engineered the mice subjects to possess a variant that would permit experimental study in conditions not comparable to what a person with Dravet syndrome would likely experience. *Id.*; Raymond Rep. at 17–18; Salgueiro-Pereira at 33. Berkovic's authors looked at SCN1A or Dravet syndrome-related patients who thought they had vaccine-induced encephalopathy (albeit in connection with a different vaccine), but it turned out they possessed SCN1A variants as well. Tr. at 104–05; Berkovic at 391. Berkovic thus (in Dr. Raymond's estimation) actually highlights how little evidence there is that genetic epilepsy is affected by an acquired or environmental factor (in comparison to the impact of the genetic mutation itself). Raymond Rep. at 18. Indeed, Berkovic acknowledged the role of genetics in epilepsy. Tr. at 103–04; Berkovic at 391.

American College of Medical Genetics and Genomics and the Association for Molecular Pathology, 17 Genetics Med. 405, 422–23 (2015), filed as Ex. B, Tab 20 (ECF No. 96-10) ("Richards"). Richards also indicates that confirmation of splice-site variant impact requires functional analysis. Tr. at 144; Richards at 409, 411. Dr. Raymond, however, deemed Richards to reflect only its authors' unsubstantiated opinion, reiterating his view that clinical geneticists properly look at the entire clinical picture, which includes genetic testing results—adding that the labs performing those tests disclose the criteria for what they report, and that these can therefore be evaluated to weigh the trustworthiness of the findings. Tr. at 143–44, 150–52.

[27] Although at trial Dr. Huq seemed to give less weight to the pneumococcal vaccine specifically as causal (in comparison to the IPV vaccine), Dr. Raymond did briefly address Dr. Huq's prior assertions that this vaccine's aluminum-based adjuvant could have played a causal role herein. Tr. at 100–01; Raymond Rep. at 13. He rejected the concept, noting that the impact of aluminum adjuvants in vaccines had been repeatedly evaluated in the past, but never shown to be pathologic. Tr. at 101. The literature Dr. Huq had cited for this was in fact an older article on aluminum toxicity in individuals who were receiving dialysis, and thus had no bearing in the context of vaccination (or the exceedingly small amounts of alum adjuvant found in vaccinees in the first place). *Id.*; Raymond Rep. at 13. Because Petitioners do not seem to rely on this aspect of Dr. Huq's opinion—and because the concept that alum adjuvants can be causal of disease has been *repeatedly rejected* in prior Vaccine Program cases—I give the issue no further time or consideration. *See, e.g., McGuinness v. Sec'y of Health & Hum. Servs.*, No. 17-0954V, 2021 WL 5292343, at *17 n.17 (Fed. Cl. Spec. Mstr. Oct. 20, 2021) (observing that the theory of autoimmune syndrome induced by adjuvants ("ASIA") has never been deemed a medically-reliable causation in any prior Program cases).

Dr. Raymond similarly contested the value of literature relied upon by Dr. Huq to establish that the pro-inflammatory impact of a vaccine could cause seizures. Dr. Huq had cited Auvin to support his contention that Dravet syndrome patients display an abnormal inflammatory reaction to vaccines. Tr. at 107–08; Raymond Rep. at 21; Auvin at e45. Auvin (evaluating the ex vivo cytokine response to a combined pediatric vaccine available in Europe) in fact *begins* by agreeing that the course of Dravet syndrome *does not change* even if its initial seizures are precipitated by vaccine. Tr. at 108; Raymond Rep. at 21; Auvin at e45. Its authors mainly wanted to determine if there was a difference in the inflammatory response following vaccination, and to do so they took monocytes (a form of white blood cells) from patients with Dravet syndrome, looking for any inflammatory response after stimulation by vaccine components and in fact observing one. Tr. at 108; Auvin at e45–46, e48–49.

But the study, Dr. Raymond contended, involved an exceedingly small sample—five patients. Tr. at 109; Raymond Rep. at 21–22; Auvin at e46.[28] Additionally, the Auvin control group subjects did not have a seizure disorder, making it difficult to draw reliable conclusions when comparing test results. Tr. at 109; Raymond Rep. at 21–22; Auvin at e46. Dr. Raymond further noted that the SCN1A gene is not expressed in monocytes, and therefore its findings specific to the inflammatory effect of vaccination alone did not say anything about how that would impact the distinguishable results of the gene mutation elsewhere. Tr. at 109–10; Raymond Rep. at 21–22. Auvin thus did not actually show that the proinflammatory impact of a vaccine would worsen or impact Dravet syndrome in a child like B.O. Tr. at 110; Raymond Rep. at 21–22.

Dr. Raymond also reacted to Riazi, which he argued conflated vaccines and infections as equal in impact, along with other sources of peripheral inflammation. Tr. at 110; Raymond Rep. at 12–13; Riazi at 36–38. Though he acknowledged that cytokines can influence, and even (in certain clinical situations) cause some seizures, he deemed it an overstatement to propose that a local inflammatory reaction to a vaccine could result in elevation in cytokines sufficient throughout the body to impact the SCN1A-effected sodium channels in the brain. Tr. at 110–11. In fact, other studies established (through animal models) that an infantile-onset form of epileptic encephalopathy (involving the SCN1A gene, moreover) could feature seizures triggered *solely* by temperature increase—without the need for any inflammation, infection, or any other triggers. *Id.*; Raymond Rep. at 10; Riazi at 37–38; J. Oakley et al., *Temperature- and Age-Dependent Seizures in a Mouse Model of Severe Myoclonic Epilepsy in Infancy*, 106 PNAS 3994, 3994, 3398 (2009), filed as Ex. B, Tab 10 (ECF No. 95-11) ("Oakley"). Based on its findings, Oakley's authors proposed the existence of "a developmentally regulated seizure susceptibility in which initial

[28] Auvin had sought to collect samples from eight patients with age-matched controls who apparently were about to undergo bone marrow transplant, but narrowed consideration to five—with no explanation on what happened to the other three, and no information on their backgrounds of the tested sample. Tr. at 108–09; Raymond Rep. at 21–22; Auvin at e46.

seizures are usually realized only with an additional provoking factor such as elevated temperature"—and that this alone was enough. Oakley at 3996–97.

Other items of literature were offered by Dr. Raymond to show the extent to which genetic causes better explained Dravet syndrome than the external impact of a vaccine. Raymond Rep. at 18. McIntosh he contended, was direct proof of the fact that vaccines *did not* likely aggravate Dravet syndrome. Tr. at 105; McIntosh at 392. McIntosh had observed that (in terms of illness development, course, or outcome) there was no identifiable difference between individuals who seized close-in-time to a vaccination, when compared to those who seized longer thereafter. Tr. at 105–06; Raymond Rep. at 18–19; McIntosh at 596–97. It relied on a cohort consisting of approximately 127 individuals, with 101 confirming they had an SCN1A variant. Tr. at 105; McIntosh at 594. Of those individuals, six were not considered, as their first seizures were absence or myoclonus, leaving 95 for the study. McIntosh at 594. The authors then looked at primary documentation to determine when the first seizure occurred, which reduced the observed group to 40 individuals. *Id.* From this group, it was observed that three patients started having seizures before vaccination, 12 experienced seizures within one day or less, and the other 25 experienced seizures over a longer timeframe when measured from vaccination. Tr. at 105; McIntosh at 594–95. Thus, vaccination per se could not be said to impact Dravet syndrome course. Tr. at 106.

Dr. Raymond also referenced a retrospective study that determined that seizure was a clinical manifestation of the natural history of the patients' genetically-determined Dravet syndrome—not that Dravet was *attributable* to environmental stimulation caused by vaccines. B. Tro-Baumann et al., *A Retrospective Study of the Relation Between Vaccination and Occurrence of Seizures in Dravet Syndrome*, 52 Epilepsia 175, 177 (2011), filed as Ex. B, Tab 30 (ECF No. 97-10) ("Tro-Baumann"). Tro-Baumann analyzed 70 German and Austrian patients—with only one third of this group experiencing seizure following vaccination. Tro-Baumann at 176. In this sub-group, seizures occurred at a median age of six months, and the seizure represented the first instance of Dravet syndrome manifestation for more than half (with most also experiencing fever, as well).[29] *Id.*; Tr. at 106–07. Tro-Baumann's authors thus found some association between vaccination and *initial* seizures (usually the first manifestation of Dravet syndrome), but emphasized that this did not establish an "assumed causal relationship" with vaccination generally, expressing concern that parents might unnecessarily avoid important vaccines on the mistaken assumption that the entire illness was vaccine-caused *ab initio*. Tr. at 106–07; Raymond Rep. at 19–20; Tro-Baumann at 177.

In advancing this position, Dr. Raymond distinguished between environmental insults that might "unmask" an existing genetic condition from truly causal impacts. If the etiologic cause for an illness like Dravet syndrome was genetic, then the cause had occurred at life's conception,

[29] Dr. Raymond noted that in Dravet syndrome, an elevated temperature is enough to cause seizure, even if it does not meet the clinical requirements for a fever. Tr. at 107.

differentiating it from the transient/intervening impact of something like a vaccine. Tr. at 137–42, 156–8l; Raymond Rep. at 20–21; Verbeek I at 663 (explaining how administered vaccines could have acted as a trigger for the first seizure, thereby unmasking the genetic predisposition); N. Verbeek et al., *Prevalence of SCN1A-Related Dravet Syndrome Among Children Reported with Seizures Following Vaccination: A Population-Based Ten-Year Cohort Study*, 8 PLoS One 1, 1 (2013), filed as Ex. B, Tab 32 (ECF No. 98-2) (indicating that vaccines can result in fever, and fevers can unmask the first seizure, but the ensuing seizure does not alter the ultimate course of disease). Thus, although a vaccine could (via its temperature-stimulatory impact) provoke a seizure event in connection with an immune response, it was not medically proper to blame the vaccine for everything that came after. Tr. at 158.

Dr. Raymond also did not detect support in the record establishing that the two vaccines B.O. received in April 2013 likely significantly aggravated his condition. Tr. at 111–12; Raymond Rep. at 24. In his view, the length of B.O.'s seizures as of April 2013 were shorter than what he experienced in December 2012 (which the record showed had been attributed to an ear infection). Tr. at 99; Ex. 19 at 74–77. Dr. Huq had maintained that B.O. was likely hypoxic after the April vaccinations (which could have contributed to the seizure impact), but Dr. Raymond discerned no evidence in B.O.'s subsequent hospitalization from this timeframe that he suffered from the effects of hypoxia.[30] *Id.* at 99, 145–48; Ex. 7 at 1. In addition, Dr. Raymond maintained, the medical record revealed the April seizures were arrested, with B.O. returning to baseline within a day and being discharged home thereafter. Tr. at 99, 156.

B.O. also had a normal MRI at this time, which was significant to Dr. Raymond because a hypoxic injury would have resulted in acute brain damage and encephalopathy, none of which were exhibited.[31] Tr. at 99–100; Raymond Rep. at 7. The imaging had been "enhanced" as well,[32] but it did not show evidence of the blood-brain barrier being open—a key point in Dr. Huq's theory. Tr. at 100, 112; Raymond Rep. at 13–14; Riazi at 38 (discussing disruption of the blood-brain barrier). There was thus no evidence of leakage, T2 weighted-image hyperintensities, flare hyperintensities, or diffusion-weighted imaging, which would go along with hypoxic ischemic

[30] Dr. Raymond did note, however, that he was uncertain of the accuracy of the pulse oximeter at that time. Tr. at 99, 145–48; Ex. 7 at 1.

[31] Dr. Raymond did not dispute that a prolonged and complex febrile seizure caused by a vaccine can, in some cases, cause sufficient brain injury to set up a *subsequent* seizure disorder. Tr. at 155–56. He also acknowledged the relevancy of the fact that B.O.'s first seizure occurred after vaccination (although that incident is not the basis for the present claim). Tr. at 154–55. However, to establish that the vaccinations at issue had harmed B.O. in a comparable manner, evidence of abnormal MRI or EEG readings would need to be shown—but is missing from this case. Tr. at 155–56.

[32] Chelated gadolinium is used as a paramagnetic contrast medium in magnetic resonance imaging. *Gadolinium,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=19531&searchterm=gadolinium (last visited Aug. 8, 2023). Enhancement permits the observation of active inflammation.

events and would show a reaction of the vaccine on the imaging. Tr. at 100. There was also no evidence of neuroinflammation or immune dysfunction. *Id.*

Finally, Dr. Raymond provided a view on the timeline of the events between the April 2013 vaccinations and subsequent seizures (as well as their relation to B.O.'s prior health). He noted that prior to this date, B.O. had already experienced three seizures (with one long seizure in December 2012, resulting in prolonged status epilepticus and associated with an ear infection), so he saw no reason to conclude that the April events were worthy of special scrutiny simply because they occurred after vaccination. Tr. at 98–99; Raymond Rep. at 14. In addition, after both his December and April events, B.O. had rapidly recovered, being discharged from in-patient care without any documentation of encephalopathy or other sequelae. Raymond Rep. at 14.

C. *Respondent's Non-Testifying Expert – Shlomo Shinnar, M.D., Ph.D.*

Dr. Shinnar, a pediatric neurologist, submitted one written expert report but did not testify. Report, dated Aug. 14, 2017, filed as Ex. A (ECF No. 66-1) ("Shinnar Rep."). Dr. Shinnar focused his opinion on diagnosis, but briefly touched upon the other *Althen* prongs. Because Respondent has not disclaimed his opinion, I summarize it below.

Dr. Shinnar received his undergraduate degree in physics from Columbia College and his medical degree from the Albert Einstein College of Medicine in the Bronx, New York. Curriculum Vitae, dated Aug. 14, 2017, filed as Exhibit B (ECF No. 64-8) ("Shinnar CV") at 1. He currently works as a Professor of Neurology, Pediatrics and Epidemiology, and Population Health at Albert Einstein College of Medicine. *Id.* at 2; Shinnar Rep. at 1. He also serves as the Hyman Climenko Professor of Neuroscience Research and the Director of the Comprehensive Epilepsy Management Center at Montefiore Medical Center and the Albert Einstein College of Medicine. Shinnar CV at 2; Shinnar Rep. at 1. Moreover, as the Director of the Comprehensive Epilepsy Management Center, he has treated and supervised the treatment of thousands of children suffering from seizure disorders. Shinnar Rep. at 1. Dr. Shinnar has also been awarded grants by the National Institute of Health to research childhood afebrile seizures as well as childhood onset epilepsy. *Id*; Shinnar CV at 5–7. He is board certified in neurology with special competence in child neurology and added qualifications in clinical neurophysiology and epilepsy. Shinnar CV at 2; Shinnar Rep. at 1. He is a licensed physician in New York. Shinnar CV at 2; Shinnar Rep. at 1.

Dr. Shinnar reiterated B.O.'s medical history and summary of important dates provided in the records before turning to the issue of diagnosis. Shinnar Rep. at 3–4. He defined epilepsy to be the occurrence of two or more unprovoked seizures separated by 24 hours. *Id.* at 5; Comm. on the Public Health Dimensions of the Epilepsies, *Epilepsy Across the Spectrum: Promoting Health and Understanding* 1, 29 (2012), filed as Ex. A, Tab 1 (ECF No. 66-2) ("Comm. on the Public Health"); Comm'n on Epidemiology & Prognosis, *Guidelines for Epidemiologic Studies on Epilepsy*, 34

Epilepsia 585, 593 (1993), filed as Ex. A, Tab 2 (ECF No. 66-3). Febrile seizures are the most common type (typically occurring during infancy or early childhood), and can be "complex" (prolonged, focal, or multiple), with complex febrile seizures associated with a higher risk of subsequent epilepsy. Nat'l Inst.'s Health, *Febrile Seizures*, 3 Consensus Dev. Conf. Summary 1, 1, 3–4 (1980), filed as Ex. A, Tab 3 (ECF No. 66-4); S. Seinfeld et al., *Febrile Seizures*, Pellock's Pediatric Epilepsy: Diagnosis & Therapy 505, 505, 507 (2017), filed as Ex. A, Tab 4 (ECF No. 66-5); A. Berg & S. Shinnar, *Complex Febrile Seizures*, 37 Epilepsia 126, 126 (1996), filed as Ex. A, Tab 5 (ECF No. 66-6). Some epilepsy syndromes, like Dravet, involve fever/temperature sensitivity. Shinnar Rep. at 5; T. Warner et al., *Heat Induced Temperature Dysregulation and Seizures in Dravet Syndrome/GEFS+ Gabrg2*$^{+/Q390X}$ *Mice*, 134 Epilepsy Res. 1, 1 (2017), filed as Ex. A, Tab 7 (ECF No. 67-1) (finding that temperature elevation alone could induce seizures in mice that have a mutated gene associated with Dravet).

Although seizures were previously classified as idiopathic, cryptogenic, or remote symptomatic, these terms have been replaced with new classifications—unknown cause, genetic/presumed genetic cause, and structural/metabolic cause. Shinnar Rep. at 5; Comm'n on Classification and Terminology of the Int'l League Against Epilepsy, *Proposal for Revised Classification of Epilepsies and Epileptic Syndromes*, 30 Epilepsia 389, 389–90 (1989), filed as Ex. A, Tab 8 (ECF No. 66-8) (explaining the old classifications of idiopathic, cryptogenic and remote symptomatic); A. Berg et al., *Revised Terminology and Concepts for Organization of Seizures and Epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009*, 51 Epilepsia 676, 680 (2010), filed as Ex. A, Tab 9 (ECF No. 66-9) (recommending new classifications for epilepsy of genetic/presumed genetic cause and structural/metabolic cause).

In Dr. Shinnar's view, B.O. was best diagnosed as having epilepsy of presumed genetic cause,[33] given the medical history and his familial history of epilepsy. Shinnar Rep. at 5–8. The prolonged seizures he had experienced were common for those with a genetically-caused epilepsy (and also not uncommon generally). *Id*. at 6; S. Shinnar, *Who is at Risk for Prolonged Seizures?*, 22 J. Child Neurology 14S, 14S (2007), filed as Ex. A, Tab 10 (ECF No. 67-2); M. Sillanpaa & S. Shinnar, *Status Epilepticus in a Population-Based Cohort with Childhood-Onset Epilepsy in Finland*, 52 Annals Neurology 303, 307 (2002), filed as Ex. A, Tab 11 (ECF No. 63-1). Also relevant to his opinion was the timing of B.O.'s first seizures, since medical science understands that children with an onset of epilepsy within the first year of life are more likely to develop intractable epilepsy and have a poorer prognosis than those diagnosed in later childhood. Shinnar Rep. at 6; A. Berg et al., *Early Development of Intractable Epilepsy in Children*, 56 Neurology 1445, 1447–451 (2001), filed as Ex. A, Tab 14 (ECF No. 63-4) (finding age to be a highly

[33] Notably, Dr. Shinnar's report was prepared and filed before either the genetic testing results discussed from the GeneDx lab, or interpretation of those results by the Duke UDN lab, had been released, and he thus assumed at the time that B.O. had tested negative for any relevant genetic mutations, but deemed that not to rule out a genetic basis for B.O.'s epilepsy. Shinnar Rep. at 5.

predictive factor for intractable epilepsy); S. Shinnar & J. Pellock, *Update on the Epidemiology and Prognosis of Pediatric Epilepsy*, 17 J. Child Neurology S4, S7–S8 (2002), filed as Ex. 65 (ECF No. 80-2) ("Shinnar & Pellock").

Dr. Shinnar also discussed the association between B.O.'s developmental issues and his epilepsy. Shinnar Rep. at 6. Cognitive difficulties and attentional issues are common comorbidities of epilepsy, although their manifestation may occur before or after a seizure disorder is observed. Shinnar & Pellock at S7–S8 (noting an increased risk for epilepsy in children with autism); D. Masur et al., *Pretreatment Cognitive Deficits and Treatment Effects on Attention in Childhood Absence Epilepsy*, 81 Neurology 1572, 1575 (2013), filed as Ex. A, Tab 17 (ECF No. 63-7) (finding an association between childhood absence epilepsy and prolonged attentional deficits); P.S. Fastenau et al., *Neuropsychological Status at Seizure Onset in Children*, 73 Neurology 526, 529–32 (2009), filed as Ex. A, Tab 18 (ECF No. 63-8) (discovering that children who had a seizure displayed more neuropsychological deficits when compared to their siblings).

Although Dr. Shinnar did not deem epilepsy a particularly rare condition, he opined that *autoimmune disorders* associated with epilepsy are uncommon. Shinnar Rep. at 6. Hallmarks of this form of epilepsy include intractable seizures and a markedly abnormal and encephalopathic EEG, with slowing as well as epileptiform activity.[34] *Id.*; C. Bien & A. Vincent, *Immune-Mediated Pediatric Epilepsies*, 111 Handbook Clinical Neurology 521, 524, 526 (2013), filed as Ex. A, Tab 21 (ECF No. 64-2); J. Suleiman et al., *Autoimmune Epilepsy in Children: Case Series and Proposed Guidelines for Identification*, 54 Epilepsia 1036, 1039 (2013), filed as Ex. A, Tab 22 (ECF No. 64-3). B.O.'s seizures, clinical course, imaging findings, and EEG were all inconsistent with the conclusion that his epilepsy had an autoimmune quality. Shinnar Rep. at 6.

Dr. Shinnar also provided his reaction to Dr. Huq's medical theory that a vaccine-induced immune response could worsen an existing epileptic disorder. Shinnar Rep. at 6–7. Although he agreed with Dr. Huq's explanation of how the immune response works, he noted that scientific literature specific to the association of cytokines with seizures usually arose in the context of evidence of damage to the hippocampal structure in the brain. *Id*; W. Gallentine et al., *Plasma Cytokines Associated with Febrile Status Epilepticus in Children: A Potential Biomarker for Acute Hippocampal Injury*, 58 Epilepsia 1102, 1102 (2017), filed as Ex. A, Tab 24 (ECF No. 64-5) (finding extreme imbalance of IL-1RA to IL-6 to be a potential biomarker of hippocampal injury). But here, as MRI imaging revealed, there was no evidence that B.O.'s brain had been impacted by seizure activity. Shinnar Rep. at 6–7. Dr. Shinnar otherwise noted that the literature associating

[34] Epileptiform activity is defined as "interictal activity on an electroencephalogram, characterized by paroxysmal spike, polyspike, or sharp wave discharges; it may occur in patients who have never had a seizure, and it does not occur in all epileptics." *Epileptiform activity,* Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=54776&searchterm=epileptiform+activity (last visited Aug. 8, 2023).

the pneumococcal vaccine with seizures is weak, and that there is no evidence of either vaccine in question causing or exacerbating epilepsy. *Id*. at 7; Rather, onset of epilepsy close to vaccination usually has a genetic or structural basis. N. Verbeek et al., *Etiologies for Seizures Around the Time of Vaccination*, 134 Pediatrics 658, 663 (2014), filed as Ex. A, Tab 26 (ECF No. 98-3) (implying that early genetic testing for children with vaccination-related onset of epilepsy as underlying genetic or structural causes were identified in 65 percent of children with epilepsy with vaccination-related onset).[35]

Ultimately, Dr. Shinnar maintained, the record in this case did not establish a connection between B.O.'s epilepsy and his April 2013 vaccinations. By that time, B.O. already had an established diagnosis of epilepsy. Shinnar Rep. at 6, 8. B.O's treating physicians did not link his epilepsy with vaccines. *Id.* at 6. This vaccination event also reflected the fourth instance in which B.O. received vaccines, with no explanation for why only one (the first) of the prior three events caused seizure. *Id.* at 7.

III. Procedural History

Petitioners filed their petition on April 4, 2016, and the matter was assigned to another special master. ECF Nos. 1, 4. Petitioners filed all relevant medical records and affidavits with the Statement of Completion by October 11, 2016. ECF No. 24. On November 29, 2016, Respondent filed a Rule 4(c) Report contesting Petitioners' right to compensation. ECF No. 28. Dr. Huq's expert report was filed by Petitioners on February 6, 2017, and Dr. Shinnar's expert report was filed by Respondents on August 14, 2017. ECF Nos. 43, 66. The matter was then transferred to another special master before getting transferred me on March 2, 2021, where I held a status conference to schedule and a two-day entitlement hearing in March 2022. ECF Nos. 73, 76. Thereafter, Petitioners filed Dr. Huq's supplemental expert report and Respondent filed Dr. Raymond's expert report in response. ECF Nos. 82, 95. The entitlement hearing was then rescheduled for September 19, 2022 and occurred on that date. ECF No. 101. After post-trial briefs were filed, the matter became ripe for determination.

V. Applicable Legal Standards

A. *Petitioners' Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table—corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table

[35] Also filed as Respondent's Ex. B, Tab 33.

Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[36] In this case, Petitioners do not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Hum. Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health and Hum. Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005): "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury."

Each *Althen* prong requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355–56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

[36] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Hum. Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Hum. Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. App'x. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Hum. Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras*, 121 Fed. Cl. at 245 ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)).

In discussing the evidentiary standard applicable to the first *Althen* prong, the Federal Circuit has consistently rejected the contention that it can be satisfied merely by establishing the proposed causal theory's scientific or medical *plausibility*. *See Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019); *LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("[h]owever, in the past we have made clear that simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." (citing *Moberly*, 592 F.3d at 1322)); *see also Howard v. Sec'y of Health & Hum. Servs*., 2023 WL 4117370, at *4 (Fed. Cl. May 18, 2023) ("[t]he standard has been preponderance for nearly four decades"), *appeal docketed,* No. 23-1816 (Fed. Cir. Apr. 28, 2023). And petitioners always have the ultimate burden of establishing their *overall* Vaccine Act claim with preponderant evidence. *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell v. United States*, 133 Fed. Cl. 782, 793 (2017) (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance standard).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

Medical records and statements of a treating physician, however, do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Hum. Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Dept. of Health & Hum. Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 F. Appx. 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must align with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 F. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for rev. den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Standard for Significant Aggravation Claim*

Where a petitioner alleges significant aggravation of a preexisting condition, the *Althen* test is expanded, and the petitioner has additional evidentiary burdens to satisfy. *Loving v. Sec'y of Health & Hum. Servs*., 86 Fed. Cl. 135, 144 (2009). In *Loving*, the Court of Federal Claims combined the *Althen* test with the test from *Whitecotton v. Sec'y of Health & Hum. Servs.*, 81 F.3d 1099, 1107 (Fed. Cir. 1996), which related to on-Table significant aggravation cases. The resultant "significant aggravation" test has six components, which require establishing:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether

> the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144; *see also W.C.*, 704 F.3d at 1357 (holding that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims"). In effect, the last three prongs of the *Loving* test correspond to the three *Althen* prongs.

In *Sharpe v. Sec'y of Health & Hum. Servs.,* 964 F.3d 1072 (Fed. Cir. 2020), the Federal Circuit further elaborated on the *Loving* framework. Under Prong (3) of the *Loving* test, A Petitioner need not demonstrate an *expected* outcome, but merely that her current-post vaccination condition was worse than pre-vaccination. *Sharpe*, 964 F.3d at 1081. And a claimant may make out a prima facie case of significant aggravation overall without eliminating a preexisting condition as the potential cause of her significantly aggravated injury (although the Circuit's recasting of the significant aggravation standard still permits Respondent to attempt to establish alternative cause, after the burden of proof has shifted to Respondent). *Id.* at 1083.

C. *Law Governing Analysis of Fact Evidence*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [ ] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (determining that it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

As noted by the Federal Circuit, "[m]edical records, in general, warrant consideration as trustworthy evidence." *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Hum. Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical

records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Hum. Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). A series of linked propositions explains why such records deserve some weight: (i) sick people visit medical professionals; (ii) sick people attempt to honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11–685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Hum. Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs*., No. 03–1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are often found to be deserving of greater evidentiary weight than oral testimony—especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Hum. Servs*., 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, the Federal Circuit has also noted that there is no formal "presumption" that records are accurate or superior on their face when compared to other forms of evidence. *Kirby v. Sec'y of Health & Hum. Servs.,* 997 F.3d 1378, 1383 (Fed. Cir. 2021). There are certainly situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility may be required when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs*., No. 90–2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the

accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y of Health & Hum. Servs*., 110 Fed. Cl. 184, 203–04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

D. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Hum. Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Hum. Servs*., 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See e.g.*, *Snyder*, 88 Fed. Cl. at 742–45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Hum. Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Expert opinions based on unsupported facts may be given relatively little weight. *See Dobrydnev v. Sec'y of Health & Hum. Servs.*, 556 F. Appx. 976, 992–93 (Fed. Cir. 2014) ("[a] doctor's conclusion is only as good as the facts upon which it is based") (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993) ("[w]hen an expert assumes facts that are not supported by a preponderance of the evidence, a finder of fact may properly reject the expert's opinion")). Expert opinions that fail to address or are at odds with contemporaneous medical records may therefore be less persuasive than those which correspond to such records. *See Gerami v. Sec'y of Health & Hum. Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013), *aff'd*, 127 Fed. Cl. 299 (2014).

E. *Consideration of Medical Literature*

Both parties filed numerous items of medical and scientific literature in this case, but not every filed item factors into the outcome of this Decision. While I have reviewed all the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioners' case—just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Hum. Servs.,* 527 F. App'x. 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

ANALYSIS

I. An Overview of Relevant Prior Decisions

There are a plethora of prior Program cases involving children with SCN1A mutations, and where a vaccine has been alleged to play a role in causing Dravet syndrome or a comparable seizure disorder. Entitlement has been consistently denied in such cases.[37] *See, e.g.*, *Oliver v. Sec'y of Health & Hum. Servs.*, No. 10-394V, 2017 WL 747846 (Fed. Cl. Spec. Mstr. Feb. 1, 2017), *mot. for review den'd*, 133 Fed. Cl. 341 (2017), *aff'd*, 900 F.3d 1357 (Fed. Cir. 2018); *Faoro v. Sec'y of Health & Hum. Servs*., 10–704V, 2016 WL 675491 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *mot. for review den'd*, 128 Fed. Cl. 61 (2016); *Barclay v. Sec'y of Health & Hum. Servs.*, 07–605V, 2014 WL 7891493 (Fed. Cl. Spec. Mstr. Dec. 15, 2014), *mot. for review den'd,* 122 Fed. Cl. 189 (2015); *Santini v. Sec'y of Health & Hum. Servs.*, 06–725V, 2014 WL 7891507 (Fed. Cl. Spec. Mstr. Dec. 15, 2014), *mot. for review den'd*, 122 Fed. Cl. 102 (2015); *Mathis v. Sec'y of Health & Hum. Servs.*, 09–467V, 2014 WL 3955650 (Fed. Cl. Spec. Mstr. July 24, 2014); *Barnette v. Sec'y of Health & Hum. Servs.*, 06–868V, 2012 WL 5285414 (Fed. Cl. Spec. Mstr. Sept. 26, 2012), *mot. for review den'd*, 110 Fed. Cl. 34 (2013); *Deribeaux v. Sec'y of Health & Hum. Servs.*, 05–306V, 2011 WL 6935504 (Fed. Cl. Spec. Mstr. Dec. 9, 2011), *mot. for review den'd*, 105 Fed. Cl. 583 (2012), *aff'd*, 717 F. 3d 1363 (Fed. Cir. 2013); *Snyder v. Sec'y of Health & Hum. Servs.*, 07–59V, 2011 WL 3022544 (Fed. Cl. Spec. Mstr. May 27, 2011), *mot. for review granted,* 102 Fed. Cl. 305 (2011), *reversed,* 553 F. App'x. 994 (Fed. Cir. 2014); *Harris v. Sec'y of Health & Hum. Servs.*, 07–60V, 2011 WL 2446321 (Fed. Cl. Spec. Mstr. May 27, 2011), *mot. for review granted*, 102 Fed. Cl. 282 (2011), *reversed,* 553 F. App'x. 994 (Fed. Cl. 2014); *Stone v. Sec'y of Health & Hum. Servs.,* No. 04-1041V, 2011 WL 836992 (Fed. Cl. Spec. Mstr. Jan. 20, 2011), *mot. for review den'd*, 99 Fed. Cl. 187 (2011), *aff'd,* 676 F.3d 1373 (Fed. Cir. 2012).

In such cases, special masters have repeatedly concluded—based on fact arguments supported by literature comparable to what was filed herein—that it is *more likely than not* that a child's seizure disorder is attributable to an SCN1A mutation (when one is discovered) than a vaccine, even if the vaccine *did* likely trigger a seizure. These determinations are consistent with the literature. Numerous articles filed in this case recognize the link between SCN1A mutations and Dravet syndrome. *See generally* L. Claes et al., *De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy,* 68 Am. J. Hum. Genetics 1327, 1327

[37] Even though (and as noted above) I am not compelled to follow the determinations in prior cases issued by my colleagues, special masters reasonably draw upon their experience in resolving Vaccine Act claims. *Doe v. Sec'y of Health & Hum. Servs*., 76 Fed. Cl. 328, 338–39 (2007) ("[o]ne reason that proceedings are more expeditious in the hands of special masters is that the special masters have the expertise and experience to know the type of information that is most probative of a claim") (emphasis added). I would therefore be remiss in ignoring prior cases presenting similar theories or factual circumstances, along with the reasoning employed in reaching such decisions.

(2001), filed as Ex. B Tab 2 (ECF No. 95-3); E. Wirrell et al., *Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel,* 68 Pediatric Neurology 18, 19 (20017), filed as Ex. B. Tab 4 (ECF No. 95-5) ("[v]ariants in the SCN1A gene . . . are found in as many as 85% of individuals who are clinically diagnosed with Dravet syndrome"); Escayg at 1652, 1656.

Such determinations, no matter how many in number, do not mean this claim should be summarily dismissed. But they stand as highly persuasive guidelines for my determination herein, since many of the same arguments advanced in this case were attempted, unsuccessfully, before. In totality, these decisions strongly underscore that existing medical science is *not* supportive of a link between Dravet syndrome and vaccines.[38]

In some of these prior cases, a claimant maintained that a vaccinated child's preexisting Dravet syndrome had been significantly aggravated by vaccination. *See, e.g.*, *Oliver*, 2017 WL 747846, at *20; *Faoro*, 2016 WL 675491, at *27. But it was consistently determined even in that context that the vaccine did not provide the "but for" explanation for the disease (regardless of whether the child's first major seizure might have been *triggered* by vaccination). *Faoro*, 2016 WL 675491, at *2 ("[a]lthough H.E.F.'s vaccinations may have caused a low-grade fever or otherwise triggered her first seizure, neither the initial seizure nor her vaccinations caused or significantly aggravated her Dravet syndrome and resulting neurological complications"); *see also Snyder/Harris*, 553 F. App'x at 1003 (finding the special master was not arbitrary in finding that petitioners' expert failed to show that the child's outcome would have been different had he not received the vaccinations at issue).

As noted above, the Federal Circuit in *Sharpe* clarified the burden placed on a petitioner arguing that a genetically-caused seizure disorder was worsened by vaccination (and in so doing arguably made it easier to meet at least the first three *Loving* prongs). *See generally Sharpe,* 964 F.3d 1072. Importantly, however, *Sharpe* did not involve an SCN1A genetic mutation, making it more akin to determinations involving genetically-related conditions that have been less studied

[38] By contrast, claimants have often succeeded in cases involving pediatric seizure disorders/epilepsy when the mutation at issue did not impact the SCN1A gene (about which far more research has been conducted). *See, e.g.*, *Thompson v. Sec'y of Health & Hum. Servs.*, No. 15-671V, 2023 WL 21234, at *32 (Fed. Cl. Spec. Mstr. Jan. 3, 2023) (involving a GABRA1 variant, and noting that McIntosh states that its findings might not apply to the 20-30 percent of patients with Dravet syndrome lacking an SCN1A mutations); *Whitehead v. Sec'y of Health & Hum. Servs.*, No. 18-1538V, 2021 WL 4946062, at *18 (Fed. Cl. Spec. Mstr. Sept. 29, 2021) (determining that petitioners were able to link child's BTRBGD mutation with the vaccines); *Sharpe v. Sec'y of Health & Hum. Servs.*, No. 14-65V, 2018 WL 7625360 (Fed. Cl. Spec. Mstr. Nov. 5, 2018), *aff'd,* 142 Fed. Cl. 630 (2019), *aff'd in part, vacated in part, remanded,* 964 F.3d 1072 (Fed. Cir. 2020) (finding that a child's pre-existing DYNC mutation, leading to seizure disorder, was nevertheless aggravated by vaccination); *but see McClellan v. Sec'y of Health & Hum. Servs.*, No. 14-714V, 2019 WL 4072130, at *25 (Fed. Cl. Spec. Mstr. July 23, 2019) (noting that a mutation in SCN8A gene resulting in seizure disorder not deemed to have been aggravated by pneumococcal vaccine, but where Respondent's experts established that gene at issue was comparable to SCN1A gene).

(and hence a context in which far less is known about the mutation-seizure disorder relationship). *Sharpe*, 964 F.3d at 1083–84. Moreover, the claimant's genetic expert in *Sharpe* was able to establish that the mutation at issue was *not* likely to be pathologic in nature. *Id.* at 1083. And the Circuit (in what amounted to its own review of the evidentiary record) found that the Respondent's expert had effectively conceded that environmental factors could unquestionably play a role in phenotypic outcomes. *Id.* at 1083–85. Most of these factors are not at play in this case (and those that are deserve less weight in this context, for the reasons discussed below).

II. B.O. Most Likely Suffers from Dravet Syndrome

In many cases, determination of the injury—or most likely diagnostic explanation for that injury—is critical to resolving the case. *Broekelschen*, 618 F.3d at 1346. This is often because a claimant's causation theory depends on proof of a particular injury, since the manner in which a vaccine is posited to cause injury would most likely manifest in a specific way. If the injury is *not* likely consistent with that proposed theory (because it is not comparable to what was alleged), the claim itself might be called into doubt.

Here, Petitioners are circumspect in identifying a diagnosis for B.O.'s illness. *See, e.g.*, Petitioners' Post-Hearing Brief, dated January 13, 2023 (ECF No. 129) ("Br.") at 1 (referring to the injury with the general phrase "underlying neurological condition"). Respondent, by contrast, more forthrightly maintains that B.O. suffers from Dravet syndrome. Respondent's Post-Hearing Brief, dated January 13, 2023 (ECF No. 128) ("Opp.") at 11 (citing Tr. at 152 (excerpt from Dr. Raymond's testimony)). This is not a case where determining which precise diagnosis the evidence best supports[39] will be fully dispositive of the claim (since Petitioners *do* argue that the environmental/external stimulus provided by vaccines could still impact the course of a Dravet syndrome patient—and/or that an SCN1A mutation is not per se predictive of pathologic outcome).

But in the context of vaccine causation, determining the most likely nature of B.O.'s injury will assist resolution of the case. And here, I find the evidence preponderates in favor of the conclusion that B.O. likely suffered from a form of Dravet syndrome that was genetic in origin.

I rely on several items of evidence from the record for this conclusion. The strongest evidence supportive of this finding is B.O.'s medical history and the clinical record of his seizure activity and related sequelae. Dr. Raymond persuasively explained why B.O.'s history reflected the kinds of symptoms seen in Dravet syndrome, and Dr. Huq at least allowed that Dravet was

[39] To be clear—*I am not proposing to diagnose B.O. myself.* Special masters are not called to do so in *any* Program case, nor are they qualified to opine on this subject. But it is within my purview to weigh the evidence, and to make a *legal* determination about facts, including what injury they best support. I may thus weigh the record in order to reach a "more likely than not"/preponderant conclusion about this topic. And that determination does not propose for a certainty what the actual and most-proper diagnosis is.

appropriately included in the diagnostic differential. The occurrence of B.O.'s seizures—first manifesting at the age of four months old, and then progressing over time thereafter, with secondary developmental issues also appearing—are all consistent with Dravet.

In addition, treater views and genetic testing results are consistent with Dravet syndrome as the most likely diagnosis. B.O. was already thought by treaters to suffer from *some* form of genetic epilepsy as early as January 2014, based on his presentation to that date. Ex. 13 at 10–11. Immediate testing did not confirm the presence of an SCN1A mutation/variant, but it was observed by September 2017, although then deemed to be of uncertain significance. Ex. 40 at 61. Then, analysis by the Duke UDN more specifically proposed that the SCN1A variant more likely than not explained B.O.'s illness, relying on his actual phenotypic presentation, and its overlap with other Dravet syndrome patients with *known* pathogenic variants, as grounds for this determination. Ex. 38 at 1597. Subsequent treaters have accepted Dravet as a diagnosis, albeit including it in a differential. And the overall medical record reveals a progressive and generally severe seizure disorder, phenotypically consistent with what a Dravet syndrome patient would experience, as Dr. Raymond persuasively established.

Petitioners have not effectively rebutted this conclusion. Dr. Huq mainly argues that the Duke UDN determination was unreliable or arbitrary, noting that GeneDx's initial assessment of the SCN1A variant was that it was of unknown significance, and that this should be given greater weight. However, the "unknown" qualification of the initial lab assessment did not preclude the possibility that the mutation is pathogenic, and it has not been shown that there is a particular reason to doubt, or give less probative weight, to the Duke UDN assessment of this data (even if admittedly the matter is not firmly resolved—and may never be). In fact, Dr. Raymond convincingly established why a mutation specific to splicing would be *likely* pathogenic, even if more research into its impact was required for greater certainty. *See* Tr. at 95–96, 124–26. Certainly, Dr. Raymond admitted (and evidence independently supports this) that a Dravet syndrome diagnosis could not solely be based on genetic testing results. But in this case the testing results serve to *corroborate* the existing clinical picture—and are consistent with it.

Dr. Huq also proposes that Lal establishes the high likelihood that SCN1A variants are routinely misclassified as pathogenic. But Lal's findings are more modest than Dr. Huq allows, as they were specific to a very limited group of identified mutations, and thus could not be credibly said to undermine all variant classification. *See* Lal at 9 ("the majority of our *investigated* SCN1A results [seven out of eight] SCN1A HGMD variants cannot be classified as clearly pathogenic," and therefore Lal's authors "*assume* that a significant fraction of patients diagnosed with pathogenic SCN1A mutations may actually not carry an SCN1A variant of relevance") (emphasis added). Dr. Raymond noted that the number of misidentified mutations was in fact probably consistent with what would be statistically expected from a large database (which in turn might contain some classifications that actually lacked good support). Tr. at 129–30; Raymond Rep. at

15–16. Moreover, articles like McIntosh (which *directly* considered the issue in this case: can vaccines worsen the course of a preexisting genetically-caused seizure disorder?) support the concept that while phenotypical presentations vary, the impact of the type of mutation might be less important than the *presence* of *any* mutation. McIntosh at 595, 597.

My weighing of the evidence on this matter thus results in the conclusion that B.O. "more likely than not" suffered from Dravet syndrome attributable to an SCN1A mutation. Petitioners are correct that the identified SCN1A mutation is not known *for certainty* to be pathogenic—but ample evidence supports the conclusion that mutations in this gene are *generally* associated with phenotypically-poor outcomes (albeit on a range) consistent with Dravet, and this plus B.O.'s own presentation, as reflected by the medical record, supports Dravet syndrome attributable to the SCN1A mutation as the most likely diagnosis.

III. Petitioners' Significant Aggravation Claim Has not Been Preponderantly Established

Below, I address only those prongs of the *Loving* test that bear on my resolution of the claim.[40]

A. *Loving Prong Four: Petitioners' Causation Theory was Unreliable And Unsupported by Sufficient Preponderant Evidence*

Because Dravet syndrome has a known genetic etiology, the Petitioners needed to establish somehow that the impact of vaccination could fuel, and thereby worsen, the course of the condition, which was already likely to be debilitating. But Dr. Huq did not persuasively accomplish this task. His theory involved the immune system's immediate, innate response to vaccination, in which production of cytokines promote inflammation while activating an immune response in other ways. He did not, however, establish that the transient, one-time effect of a vaccine would be enough to cause pathogenic amounts of cytokines to negatively impact and worsen an existing

[40] Had I needed to do so, however, I would have found that Petitioners could meet the first three *Loving* prongs. B.O. clearly had some form of epilepsy that was most likely genetic in origin prior to the April 2013 vaccinations; his seizure disorder progressed, and he displayed a number of developmental issues, thereafter; and it is reasonable to conclude his health overall had worsened *after as opposed to before* the April 2013 vaccinations (although the record does also show that B.O. experienced some non-vaccine-related seizures prior to this time).

The sixth *Loving* prong presents a slightly more difficult question. The immediate timeframe for seizures occurring after receipt of the April 2013 vaccines (the day after) was reasonable, and even foreseeable (since it was known to B.O.'s treaters that vaccination might stimulate seizure activity—hence the recommendation he receive prophylactic doses of anti-seizure medications before being vaccinated. Ex. 13 at 70. It is less clear, however, what timeframe *would* be expected for worsening of a genetically-associated or caused epilepsy due to vaccine-induced seizures, or whether the tempo of B.O.'s course thereafter is consistent with it. But because I do not find the significant aggravation "can cause" or "did cause" prongs were met, I do not reach this prong.

seizure disorder—even if the impact of vaccination *could* trigger transient seizures close to the vaccination event (as the record establishes occurred here).

A primary deficiency of this theory is the degree to which it assumes the one-time effect of a vaccine in stimulating production of cytokines will in turn contribute to a pathogenic process that predated the vaccination. Program petitioners often advance theories that upregulation of cytokines by vaccines can become pathogenic in some manner—but more often than not, such theories are found wanting, especially to the extent they over-rely on expected vaccine function to form the basis for a causation theory. *See Olson v. Sec'y of Health & Human Servs.*, No. 13-439V, 2017 WL 3624085, at *20 (Fed. Cl. Spec. Mstr. July 14, 2017) (deeming it speculative to purport that cytokine upregulation due to a vaccine "would be robust enough, and occur for long enough, to be pathogenic generally, let alone to cause" the complained-of injury), *mot. for review den'd*, 135 Fed. Cl. 670 (2017), *aff'd*, 758 F. App'x 919 (Fed. Cir. 2018). The theory as presented in this case was no more persuasive. Indeed, given the extent to which this *same* kind of theory has previously been rejected in the context of Dravet syndrome cases deemed associated with an SCN1A mutation, more recent scientific or medical evidence undermining the medical consensus on this topic would be required—but was not offered. *Oliver*, 2017 WL 747846, at *20; *Faoro*, 2016 WL 675491, at *2, 27.

This is not to say that Petitioners' theory was wholly lacking in plausibility. Dr. Huq did credibly establish that environmental factors *can* play some role in the course of an otherwise genetically-caused illness—a contention that Dr. Raymond at times reluctantly admitted (and that is reflected in many items of literature filed by both sides in this case). The causation theory presented also established that individuals with a seizure disorder like Dravet syndrome can anticipate difficulties in reaction to vaccination, and may well experience seizure activity after receipt of vaccines (as in fact appeared to happen to B.O. both in July 2012 and April 2013).

But *this does not mean* that the impact of a vaccine on a person with Dravet "more likely than not" wholly alters the course of their disease, or that "but for" vaccination Dravet syndrome will be less catastrophic. Not enough evidence specific to the context herein was offered to show that the peripheral, temporary inflammatory impact of vaccination *will likely* also worsen a seizure disorder emanating from the brain; items like Hervé are too general, while Riazi confuses the role of cytokines in seizures with *cause* (and Dr. Raymond otherwise persuasively rebutted its value herein). Otherwise, there is a gulf between a situation in which a person with an existing, genetically-determined seizure disorder suffers a seizure due to vaccination, versus where the seizure can be shown to have caused an injury that *later* worsened a child's health. *See, e.g.*, *Weaver v. Sec'y of Health & Hum. Servs.*, No. 16-1494V, 2022 WL 12542485 (Fed. Cl. Spec. Mstr. Sept. 23, 2022), *reversed in part, vacated in part,* 164 Fed. Cl. 608 (2023), *remanded,* 2023 WL 3836239, at *2 (Fed. Cl. May 8, 2023) (determining on remand that vaccines induced a febrile seizure that caused and significantly aggravated the child's seizure disorder; no evidence of an

underlying genetic cause for the disorder had been supplied); *Ginn v. Sec'y of Health & Hum. Servs.,* No. 16-1466V, 2021 WL 1558342 (Fed. Cl. Spec. Mstr. Mar. 26, 2021) (finding that five vaccines, including the flu vaccine, triggered a febrile seizure in four-year-old that contributed/led to development of epilepsy).[41]

The medical and scientific literature offered in this case does not support the conclusion that a vaccine-induced seizure occurring in the context of a genetically-initiated seizure disorder can worsen the underlying condition. On the contrary—some items of evidence directly contradict that contention. *See generally* McIntosh,[42] Tro-Baumann. Petitioners offered nothing so directly on point in response—and although it is a truism in Program cases that claimants can prevail without direct evidence, and need not otherwise offer it, when *Respondent* marshals direct evidence rebutting causation against them, it becomes unlikely that a collection of loosely-linked contentions about cytokines and possible but uncorroborated environmental impacts on seizure disorders will carry the day.

I also do not find that *Sharpe* compels a different outcome. Far more is known about SCN1A mutations, and their likely relationship to Dravet syndrome, than mutations in other genes, such as the one found to exist in that case. Moreover, the *Sharpe* claimant had the benefit of expert testimony from a geneticist, who attempted mightily to show that the mutation at issue was not likely pathologic. *Sharpe*, 964 F.3d at 1083–85. Here, by contrast, although Dr. Huq offered the general view that "not all" SCN1A mutations can be assumed pathogenic, he did not rebut the Respondent's contention that as a general matter, the mutation herein explains better the cause of Dravet than a transient, vaccine-caused seizure. Otherwise, not enough is known about how environmental factors interact with such a mutation to deem them "more likely than not" capable of aggravating what would otherwise be expected to be a severe condition—and Dr. Raymond herein certainly did not concede that vaccination could play such a role in any event.

Parallel arguments were advanced in this case about whether the precise *nature* of the SCN1A mutation that B.O. possesses was more, or less, likely to result in Dravet syndrome, as opposed to a less-catastrophic form of epilepsy. Dr. Huq accurately observed that the precise nature of the mutation at issue is not known, and the evidence shows a range of possible phenotypic outcomes, further suggesting that some mutations are less pathogenic than others. Dr. Raymond

[41] By contrast, and as noted above, prior case law does not even support a contention that a child who *first* experiences vaccine-induced seizures, but is later deemed to suffer from Dravet syndrome, can establish causation. For this reason, Petitioners could not have succeeded even if their case had focused only on the July 2012 seizures—which were also experienced after vaccination, but were the first such seizures B.O. experienced—as the basis for the claim. (Of course, since this matter was initiated in 2016, such a claim would be time-barred).

[42] McIntosh, which is specific to the context of SCN1A mutation in Dravet syndrome, has been deemed persuasive in many prior comparable decisions. *Oliver*, 2017 WL 747846, at *14, n.32, 20, 24; *Barclay*, 2014 WL 7891493, at *17; *Barnette*, 2012 WL 5285414, at *11, 16.

persuasively established, however, that the nature of the mutation—which would impact splicing—was *likely* to be pathogenic, even if testing had not identified the mutation's impact with certainty.

In resolving this dispute, I deemed Dr. Raymond's testimony on this matter more compelling and convincing than Dr. Huq's responses. My weighing of the competing expert opinions is *wholly consistent* with my charge as special master, which does not obligate me to accept expert testimony wholesale, merely because it is offered on a petitioner's behalf. As noted in *Sword v. United States*, 44 Fed. Cl. 183, 188 (1999),

> [e]ven more than ordinary fact-finders, this Court has recognized the unique ability of Special Masters to adjudge cases in the light of their own acquired specialized knowledge and expertise . . . The Special Master's sole professional responsibility for years has been to preside over vaccine cases . . . No judge or jury can be forced to accept or reject an expert's opinion or a party's theory at face value. To require such a choice in this context is to neglect the Special Master's duty to "vigorously and diligently investigate the factual elements" underlying the petition.

All in all, it is *not* "more likely than not" that vaccines could worsen a case of Dravet syndrome attributable to an SCN1A mutation—even if the precise nature of the mutation itself cannot be identified with certainty.

B. *Loving Prong Five: B.O.'s Vaccines Did Not Likely Worsen His Epileptic Seizure Disorder/Dravet Syndrome*

The medical record does not support the conclusion that B.O.'s Dravet syndrome was impacted negatively by the April 2013 vaccination event. First, no contemporaneous treaters so concluded. At best, they recognized the general concept that vaccination could promote transient seizure activity, and in fact this appears to have occurred to B.O. But the record does not include contemporaneous treater opinions that his subsequent course was likely worsened by this occurrence.

Second, there is no identifiable record evidence that B.O.'s post-vaccination seizure event caused some identifiable form of brain injury that later played a role in the course of his Dravet syndrome. Ex. 18 at 757. Dr. Huq's contentions about hypoxia were not corroborated with imaging proof, such as MRI results confirming the existence of active inflammation close-in-time to vaccination. Ex. 18 at 757. In fact, the testing performed around the time of the vaccinations at issue does not corroborate the theory. Ex. 18 at 757 (April 19, 2013 MRI results). This case is thus unlike *Ginn,* in which evidence of brain damage in the close-in-time wake of vaccination was provided or existed. *Ginn*, 2021 WL 1558342, at *10.

Finally, the record does not more broadly support the conclusion that the vaccine-induced seizures B.O. experienced in April 2013 constituted an inflection point, after which time his overall course worsened *due* to those vaccines. Rather, as Dr. Raymond persuasively explained, the progression of B.O.'s disorder—beginning before vaccination, and including what the record shows transpired after—is consistent with the medical understanding of how Dravet syndrome usually unfolds. *See, e.g.*, C. Dravet, *The Core Dravet Syndrome Phenotype,* 52 Epilepsia 3, 6 (Suppl. 2) (2011), filed as Ex. B Tab 1 (ECF No. 95-2) ("Dravet") (describing overall course from onset through five years of age and beyond). Indeed, Dravet (authored by the very individual whose name has been given to the disorder) specifically characterizes years one to five as the "worsening" stage, featuring "frequent seizures and statuses, behavioral deterioration, and neurologic signs"—exactly consistent with what B.O. (who was 13 months old in April 2013) experienced. Dravet at 6. The vaccines given at this time only bore a temporal relationship to his subsequent symptomology.

I thus do not give great weight to the manifestation of B.O.'s developmental issues post-vaccination as evidence that the vaccines likely worsened his course. These bear no more than a temporal association to vaccination, and are not inconsistent with the timeframe in which a child suffering from this disorder would begin to manifest developmental issues. Persuasive prior decisions support this view. *See e.g.*, *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014) (holding that "the basis for Ms. LaLonde's petition reduces to a temporal relationship between the administration of the DTaP vaccine and M.L.'s focal brain injuries. As we have stated before, a temporal correlation alone is not enough to demonstrate causation."); *Anderson v. Sec'y of Health & Hum. Servs.*, No. 02-1314V, 2016 WL 8256278, at *27 (Fed. Cl. Spec. Mstr. Nov. 1, 2016), *mot. for review den'd*, 131 Fed. Cl. 735 (Fed. Cl. May 5, 2017), *aff'd,* 717 F. App'x 1009 (Fed. Cir. 2018) (denying petitioners' request for compensation in an autism case due to the lack of association between vaccination and injury, despite post-vaccination manifestation of developmental issues).

IV. Respondent Has Established a "Factor Unrelated" to Vaccination as Causal

For the reasons stated above, I do not find that Petitioners carried their prima facie burden—and therefore the burden of proof never shifted to Respondent to prove a "factor unrelated" to vaccination. However, in the event it had been found that Petitioners did show that (a) vaccines via stimulation of the innate immune response *could* worsen an "underlying neurological disorder," and (b) B.O.'s April 2013 vaccines did do so, I would find that Respondent preponderantly established a genetic explanation for the course of B.O.'s epileptic condition—and that the vaccines can be ruled out herein as contributing to it.

After a claimant successfully establishes a prima facie case of causation, "the burden then shifts to the government to prove alternative causation by a preponderance of the evidence." Section 13(a)(1)(B); *Cedillo,* 617 F.3d at 1338; *Schilling v. Sec'y of Health & Hum. Servs.*, No. 16-527V, 2022 WL 1101597, at *21 (Fed. Cl. Spec. Mstr. Mar. 17, 2022). The Vaccine Act defines "factors unrelated to the administration of the vaccine" to be matters "documented by the petitioner's evidence or other material in the record, include infection, toxins, trauma (including birth trauma and related anoxia), or metabolic disturbances which have no known relation to the vaccine involved, but which in the particular case are shown to have been the agent or agents *principally responsible for causing* the petitioner's illness, disability, injury, condition, or death." Section 13(a)(2)(B) (emphasis added).

The Respondent's burden in this context is distinguishable from what a petitioner must meet. As noted by the Court in *Stone v. Sec'y of Health & Hum. Servs.*, 95 Fed. Cl. 233, 237 (2010),

> the standard for proving a "factor unrelated" is higher than the petitioner's burden of proving a prima facie case. Although a petitioner is required to show that the vaccine was a "substantial factor" in causing his or her injury, "the petitioner need not show that the vaccine was the sole or predominant cause of her injury." (*de Bazan,* 539 F.3d at 1351). The respondent's burden, by contrast, is to "identify[ ] a particular [unrelated] factor (or factors) and present [ ] sufficient evidence to establish that it was the *sole substantial factor* in bringing about the injury." *Id.* at 1354 (emphasis added). In order to prevail, therefore, the respondent must "exclude[ ] the vaccine as a substantial factor."

Id. The *Stone* panel went on to observe that "[t]he difference between "substantial factor" and "sole substantial factor" is a meaningful one," noting that compensation could still be awarded even in cases where a factor unrelated had been shown to be substantial—but not "solely" substantial. *Stone,* 95 F.3d at 237 n.5 (citations omitted). Thus, the obligation placed on Respondent to prove a factor unrelated goes beyond what a petitioner need show under *Shyface*—and, as *Stone* explains, actually shines light on the nature of the *Shyface* inquiry (since Petitioners prevail in a "two cause" case even when they cannot prove the vaccine was the main cause of injury).

Importantly, the additional duties placed on Respondent in proving factor unrelated do not also include imposition of a heightened *evidentiary* burden. Evidence deemed *sufficient* to conclude that a factor unrelated has been demonstrated must only be *preponderant*—Respondent is no more obligated to prove factor unrelated to a degree of certainty than a petitioner is when offering evidence on the *Althen* prongs. Thus (under the "fifty percent and a feather" colloquial summation of the preponderance standard), Respondent can prove a factor unrelated caused an injury, to the exclusion of the vaccine, *even* if some doubt persists as to whether it is *certain* the vaccine was not also causal.

In practice, special masters have found the factor unrelated burden has been satisfied based on the same mix of evidence and weighing of items of literature versus expert testimony that occurs when evaluating a petitioner's initial, prima facie success. In *Stone,* for example, (where Respondent maintained that a child's Dravet syndrome was solely due to a genetic mutation rather than vaccination) the Court found that the special master had applied the wrong evidentiary standard in evaluating factor unrelated, remanding the case so the analysis could be performed again. But on remand, the special master was readily able to conclude that Respondent had met his burden, relying on a showing that included (a) the determination to give more weight to Respondent's expert testimony than the petitioner's, (b) the highly persuasive evidence of the alternative cause, and (c) an absence of record evidence that the vaccine *itself* had caused any harm to the child's brain (as would needed to have been shown to conclude the vaccine caused injury in accordance with the theory alleged). *Stone*, 2011 WL 836992, at *3, *mot. for review den'd*, 99 Fed. Cl. 187 (2011), *aff'd,* 676 F.3d 1373 (Fed. Cir. 2012).

Here, as in *Stone,* the evidence offered in this case strongly supports the conclusion that B.O.'s SCN1A mutation was "more likely than not" causal of his Dravet syndrome post-vaccination, with the vaccines excluded as causing no more than a transient set of seizures that do not also explain his subsequent condition. There is, again, no corroborative evidence of these seizures harming him in his brain such that subsequent seizure activity would be made worse—contrasted with ample evidence, some of it supplied by Dr. Raymond, about what outcomes and courses a child with Dravet syndrome would experience. The evidence of an environmental factor as playing a role in a genetically-caused disorder or illness is too general and nonspecific to the transient effect of vaccination in stimulating an innate immune response. And existing research on the subject of the environmental impact of vaccines on a child with Dravet syndrome suggests that the vaccines will not fundamentally or meaningfully alter the likely course of the condition, even if they can spark a transient seizure.

CONCLUSION

It is always disheartening when the evidence compels a special master to deny entitlement in a case involving a child, and where the record unquestionably shows that the relevant vaccination event was followed by severe illness. Under such circumstances, the temptation to grant entitlement is high, especially since doing so would aid worthy individuals like the Osenbachs, whose loving struggles in their care of B.O. are self-evident.

But it is axiomatically the case in the Program that not all post-vaccination injuries are vaccine caused. Nor can vaccines be deemed causal of a pre-existing injury (and one with an identified and highly likely genetic cause, as well). Under such circumstances, Petitioners cannot merely point to an intervening vaccine event, followed by evidence that an already-ill child's

condition progressed after that point, and deem the two causally related. They must instead preponderantly show that a vaccine *could worsen* the injury, and likely did so, with reference to reliable and compelling evidence.

At bottom, Petitioners' case relies on finding that vaccines received in the midst of an existing, genetically-caused seizure disorder were causal of what followed. But the record does not support such a finding. I therefore must DENY entitlement in this case.

In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court **SHALL ENTER JUDGMENT** in accordance with the terms of this Decision.[43]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Chief Special Master

[43] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment if (jointly or separately) they file notices renouncing their right to seek review.